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SOME TRANSFORMATIONS OF MALEO- AND FUMAROPIMARIC ACIDS.

by

Charles Emmons McDonald

B. Sc.

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY.

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EDMONTON, ALBERTA

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UNIVERSITY OF ALBERTA
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend
to the Faculty of Graduate Studies for acceptance, a thesis entitled,
SOME TRANSFORMATIONS OF MALEO- AND FUMAROPIMARIC ACIDS,
submitted by Charles E. McDonald, in partial fulfilment of the require-
ments for the degree of Doctor of Philosophy.

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ABSTRACT

A long range shielding of the C-17 angular methyl in methyl maleopimarate (28b) caused by the $\triangle^{7,8}$ olefinic double bond has enabled the assignment of a trans-anti configuration to maleopimaric acid thereby confirming the presence of this same ring system in levopimaric acid 26a.

The anhydride function of maleopimaric acid has been removed by an oxidative bisdecarboxylation of the derived diacid 42 with lead tetraacetate in pyridine and the isopropyl group removed by ozonization to give the ketone 38 which was further degraded by Baeyer-Villiger oxidation.

The C-1 gem dimethyl analog of maleopimaric acid has been prepared by Diels-Alder addition of maleic anhydride to abieta 7,14 (9)-diene and has been converted to the hydrocarbon 71 utilizing the methods developed in the maleopimaric acid series'. The hydrocarbon was found to bear an enantiomeric relationship to the hydrocarbon 76 derived from atisine. This result enabled us to confirm the assignment of both the relative and absolute configuration of atisine and related diterpene alkaloids.

The chemical shift values of the C-17 methyl group in a number of maleopimaric acid derivatives have been tabulated. These values fall into three groups: 1) ca. 9.37 τ for $\triangle^{7,8}$ derivatives; 2) 9.20 τ for compounds containing an exocyclic double bond at C-7 and 3) 9.05 τ for saturated derivatives. In addition, a $\triangle^{7,8}$ olefinic bond has been found to shield endo carbomethoxyl groups by ca. 0.05 p.p.m.. Finally, a

mutual shielding of eclipsed carbomethoxyl groups has been observed.

The bisdecarboxylation of methyl fumaropimarate (42) with lead tetraacetate has been found to yield four lactones in addition to the diene 40. The results which led to the elucidation of the structure for three of these lactones are presented along with speculation on their mode of formation.

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1. STEREOCHEMISTRY OF ATISINE AND RELATED BASES.

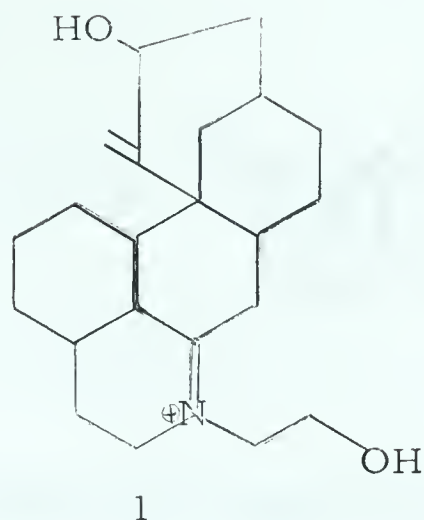
A. INTRODUCTION

The aconite alkaloids, a term originally applied to alkaloids of the genera Aconitium and Delphinium¹ but later expanded to include the structurally related Garrya alkaloids² can be divided into two broad categories: the aconitines and the atisines³.

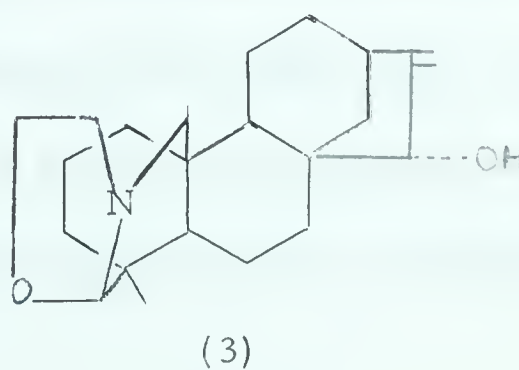
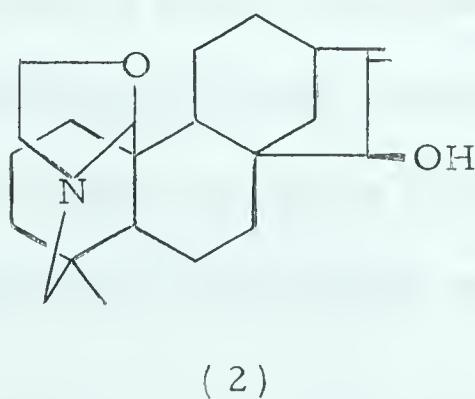
The aconitines are highly toxic, highly substituted ester bases possessing a C-19 carbon skeleton whose complex structures are known partly from the results of X-ray crystallography^{4a} and partly from chemical studies^{4b}.

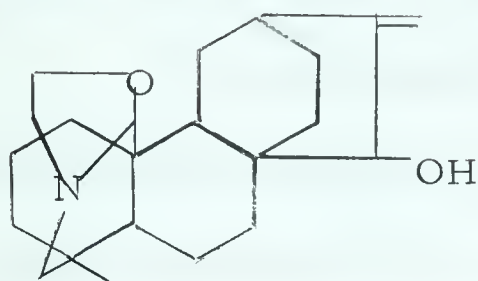
The atisines or "simple" alkaloids are relatively non-toxic amino alcohols possessing a C-20 carbon skeleton and few substituents. The most prominent member of this group, atisine, was given its name by Broughten in 1877⁵, and after sixty years of study, much of which has been described as of little more than historical interest⁶, its correct molecular formula was determined as $C_{22}H_{33}NO_2$ ⁷.

In 1951, after fifteen years of investigation on atisine, W. A. Jacobs and co-workers, although unable to reach any final conclusion concerning its structure, had accumulated a considerable body of experimental data, and were in a position to propose the tentative structure (1)⁸.

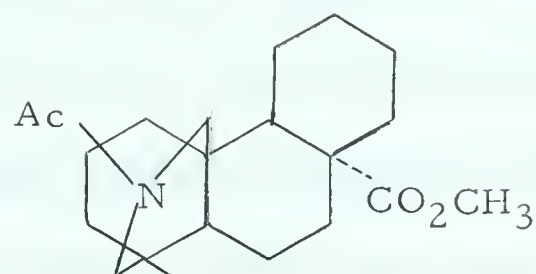


At about this time, Wiesner and co-workers initiated studies on the two *Garrya* alkaloids, veatchine and garryine, and by 1954 had established the structures (2) and (3) for these alkaloids⁹. Soon after, the close parallel found to exist between the chemistry of these bases on the one hand, and atisine on the other, led Wiesner and colleagues to suggest the revised structure (4) for atisine¹⁰ - a proposal which has since been fully confirmed by the detailed investigations of O. E. Edwards at the National Research Council in Ottawa^{11,12,12a} and S. W. Pelletier at the Rockefeller Institute, New York¹³ on atisine and the closely related alkaloids ajaconine and atidine, and by the correlation of atisine with the *Garrya* alkaloids through the degradation product 5¹⁴.





(4)



(5)

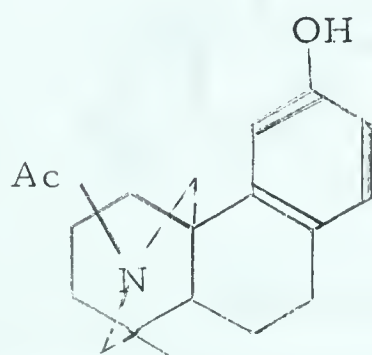
With the gross structural features of the atisine alkaloids secured, the remaining problem of defining their relative and absolute configuration came in for increasing attention. In this connection, the studies on ajaconine have been central to the early discussions on the relative stereochemistry of the perhydrophenanthrene ring^{12,15,16}.

Summarized briefly, the arguments are as follows. First, the facile formation of a C9-C17 ether bridge in ajaconine requires that the A:B rings be trans fused. The anti arrangement of ring C follows from two observations. First, the large molecular rotation difference which accompanies opening of the C-9, C-17 ether link in ajaconine is paralleled by the conversion of ring B from a boat to a chair conformation in a trans-anti-ring system; whereas, in a trans-syn fusion, the ring is still restricted to a boat conformation by the adjacent rings, and consequently only a minor conformational change, the removal of an element of distortion in the ring, accompanies opening of the oxide ring. Secondly, spectral properties of the C-9 hydroxy and acetoxy derivatives indicate that epimers in the original α configuration, cis to C-17, are equatorial.

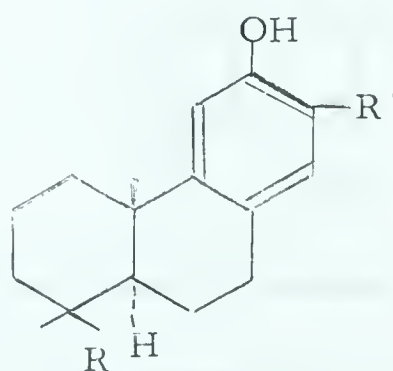
This orientation is only possible with a trans-anti backbone, the trans-syn alternative requiring an axial orientation for the α epimers.

Corroborating evidence is found in the facile isomerization of atisine and veatchine to isoatisine and garryine respectively and in the higher basicity of the former pair relative to the rearranged isomers. Both phenomena have been rationalized in terms of a steric interaction between the oxazolidine oxygen and hydrogen on C-5^{17,18}, an explanation which is only valid in a trans-anti-ring system, since this interaction is absent in the trans-syn system.

First indication that the atisine alkaloids possessed an absolute stereochemistry antipodal to that normally encountered in the diterpenes, came with the degradation of atisine to the phenol 6¹¹ and comparison of its molecular rotation ($M_D = -314^\circ$) with those of ferruginol (7b) ($M_D = +117^\circ$), methyl 6-hydroxydehydroabietate (7a) ($M_D = +234^\circ$) and podocarpic acid ($M_{Hg} = +396^\circ$) all of which possess the steroid configuration (part structure 7).

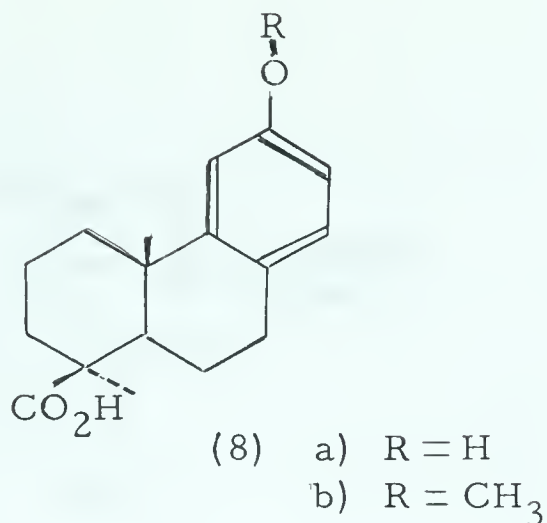


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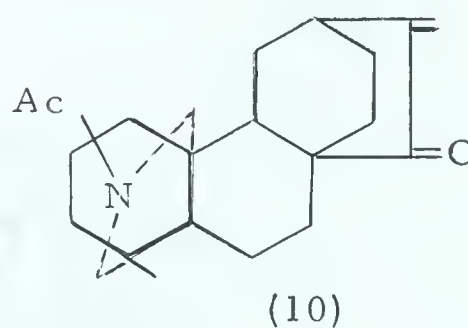
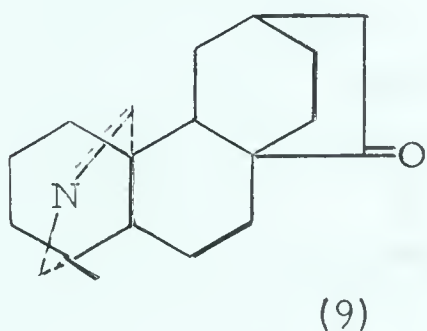


(7) a) $R = CO_2CH_3$; $R' = H$
b) $R = CH_3$; $R' = iPr$

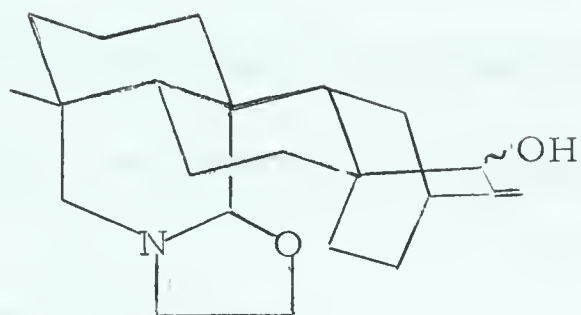
More recently, this conclusion has been confirmed by the six step transformation of the methyl ether of podocarpic acid (8b) into the enantiomer of 6¹⁹ ($M_D = -332$).



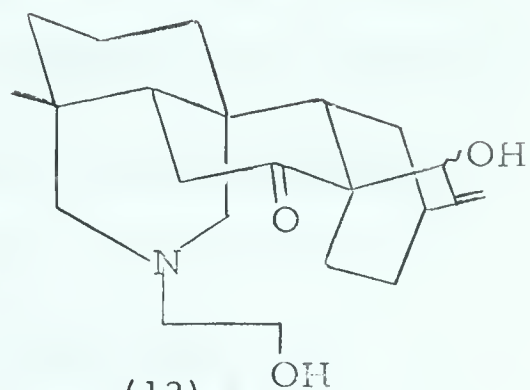
The remaining task of placing the allylic alcohol on the bicyclo-octane bridge, trans to the nitrogen, was accomplished by observing that reduction of the ketones 9¹¹ and 10¹³ with lithium aluminium hydride yielded approximately 1:1 mixtures of alcohols epimeric at C-8. In view of the severe crowding known to exist between C-17 and C-19 it is unlikely that such epimeric mixtures would result from C-19 ketones and consequently, it is similarly unlikely that the allylic alcohol system from which they are obtained is located on the cis ethano bridge.



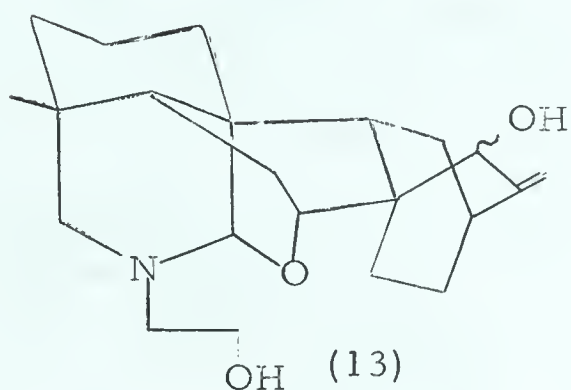
With this final problem resolved it became possible to represent the structure of atisine and the chemically interrelated alkaloids atidine, ajaconine, veatchine, garryfoline, garryine, and cuauchichicine in terms of the stereoformulae (11-17) respectively.



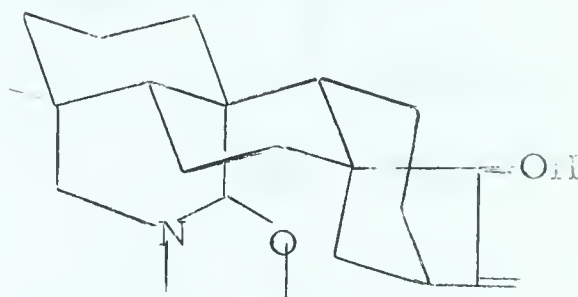
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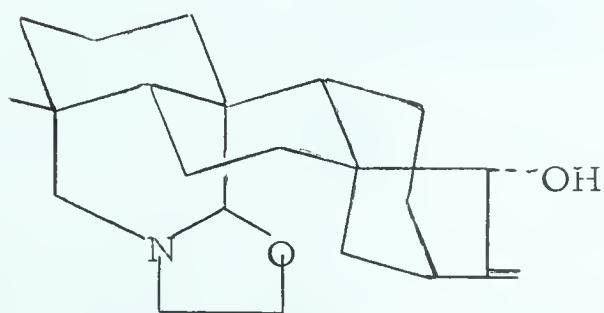
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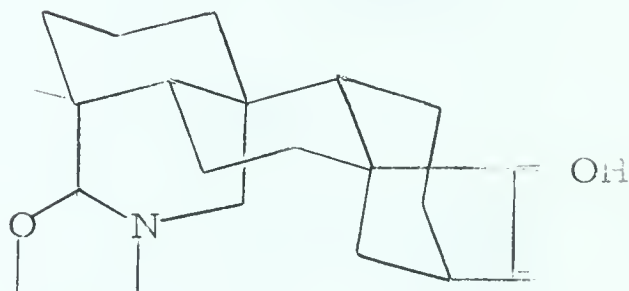
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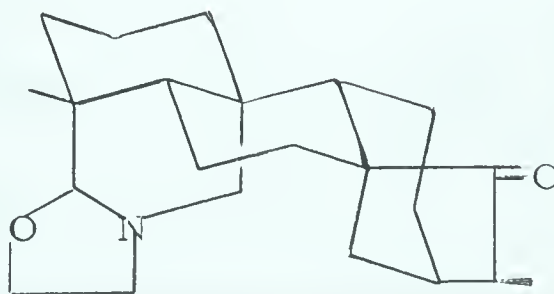
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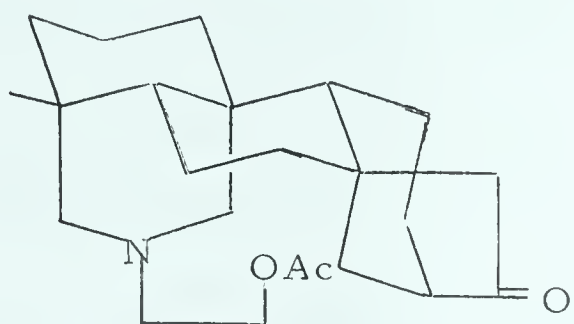
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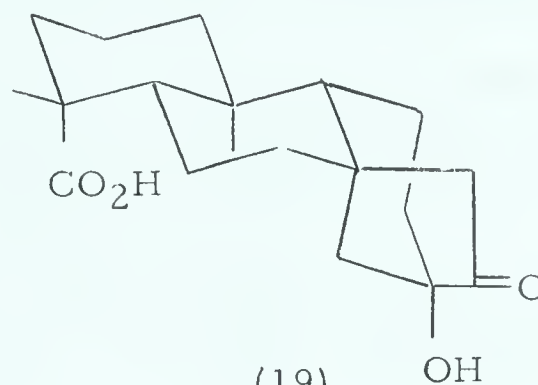
(17)

Recently, rotatory dispersion studies on the veatchine and garryfoline derivative 18²⁰, the important interrelation of garryfoline with steviol (19)²¹ and kaurene (20)²² through the hydrocarbon 21²⁰, and application of the octant rule to the steviol derivative (22)²³ have provided

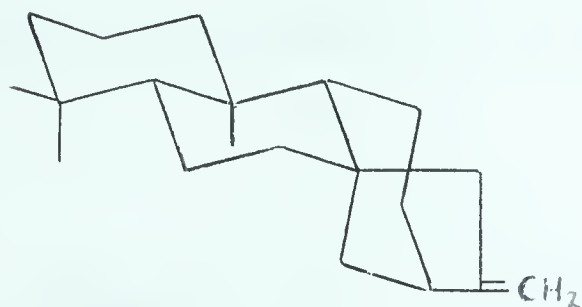
not only the first experimental connection of these diterpene alkaloids with the phyllocladene-type diterpenes, but in addition have confirmed the absolute configuration at carbons 8, 9 and 13 in these alkaloids.



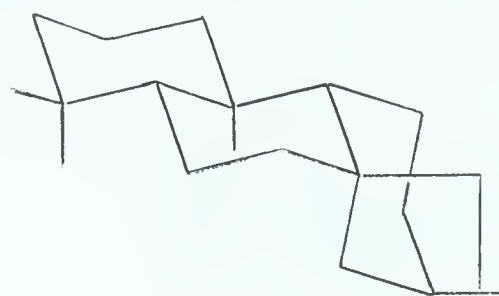
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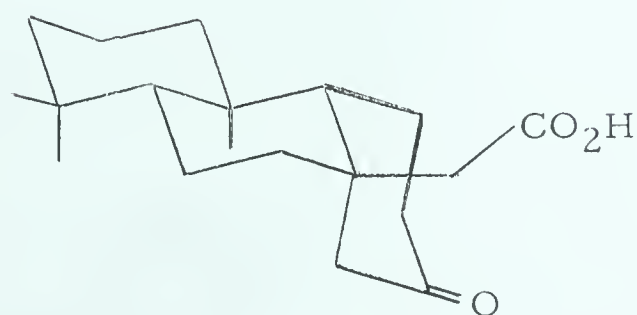
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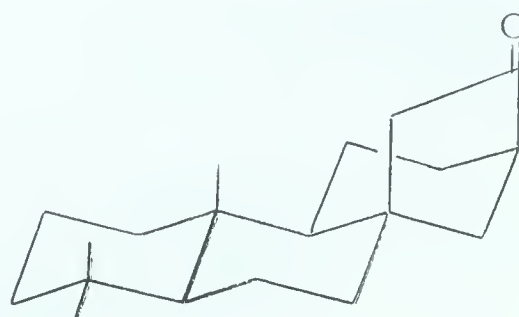
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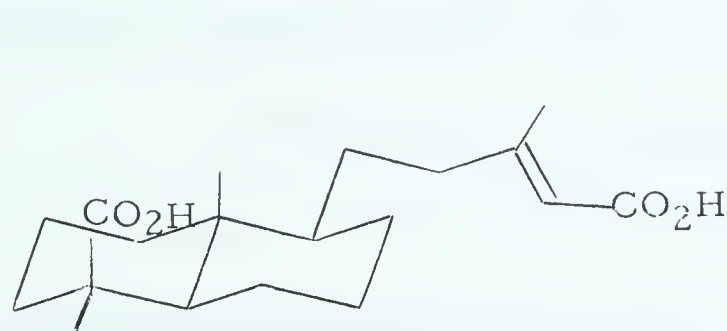


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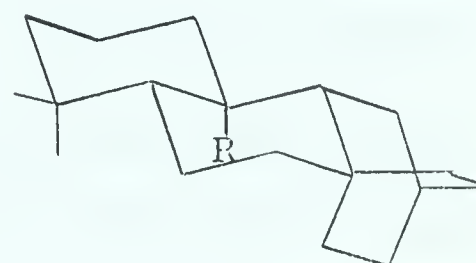
The evidence relating to the absolute configuration at C-8 and C-13 is based on the positive Cotton effect of 18, identical in sign and similar in amplitude to the phyllocladene derivative 23.

Application of the octant rule to the negative Cotton effect shown by the steviol derivative (22) similarly provided RD confirmation for the configurational assignment at C-9 of these alkaloids.

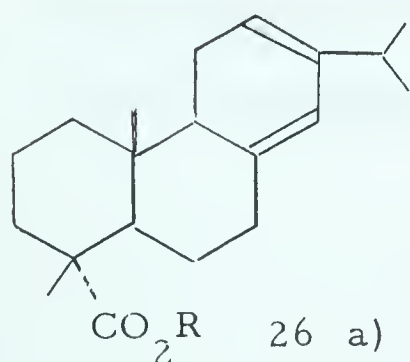
When studies on the stereochemistry of atisine were initiated in this laboratory (1959), the gross structures of all seven alkaloids had been established, and soon after, with the conversion of atisine and veatchine to the common degradation product (5), the chemical interrelation of these alkaloids was completed. The correct relative and absolute stereochemistry had been suggested (reference 17) and confirmation was being sought in an attempted interrelation of atisine with agathenedicarboxylic acid (24), a diterpene of established configuration, through the degradation product 25²⁴.



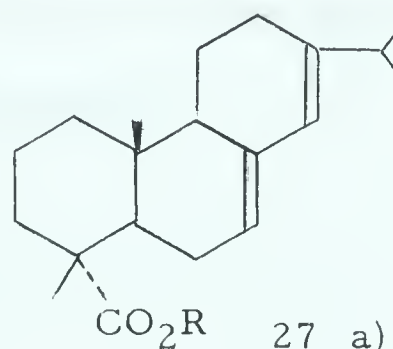
24



25 a) $R = CH_2OH$
b) $R = CO_2H$



26 a) $R = H$
b) $R = CH_3$



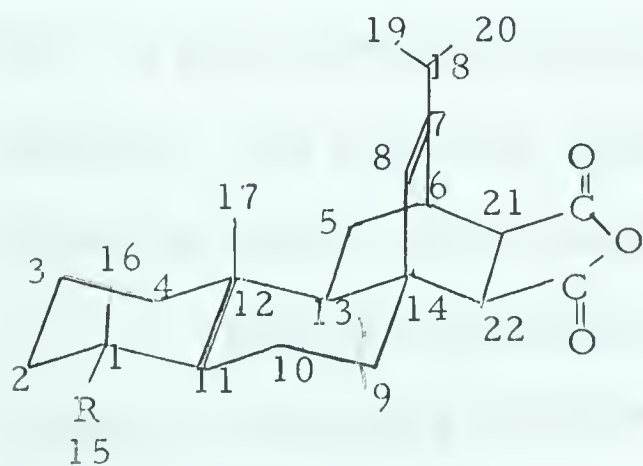
27 a) $R = H$
b) $R = CH_3$

It occurred to us that this correlation might also be possible employing the diterpene levopimaric acid (26a) or its double bond isomer, abietic acid (27a). The configuration of the A:B ring fusion in these acids was known to be identical with that possessed by the steroids²⁵, and

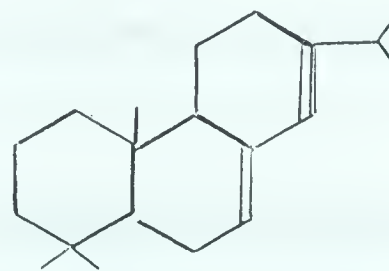
although the configuration at C-9 was still being disputed^{25,26}, evidence was soon forthcoming both from this and other laboratories^{27,28,29,30} which established the trans anti backbone necessary for a successful correlation.

The Diels-Alder reaction of levopimaric and abietic acid with maleic anhydride has been known for some time³¹ and the product, maleopimaric acid (28a), occupies an important position in the structural investigation of the resin acids³². For our purposes the value of this reaction lay in the fact that it provided a simple route to the tetracyclic skeleton of atisine and the related alkaloids, ajaconine and atidine.

A discussion of the experimental results falls naturally into two categories. First, initial studies on the commercially available maleopimaric acid (28a) which led to the development of methods for removing the anhydride and isopropyl groups, and secondly, a subsequent extension of the Diels-Alder reaction to abieta-7,14(9)-diene (29), and application of these methods to the resulting gem-dimethyl adduct 30 for the actual correlation with atisine.



- 28 a) R = CO₂H
 b) R = CO₂CH₃
 30 R = CH₃



29

B. RESULTS AND DISCUSSION.

I. STRUCTURE OF MALEOPIMARIC ACID.

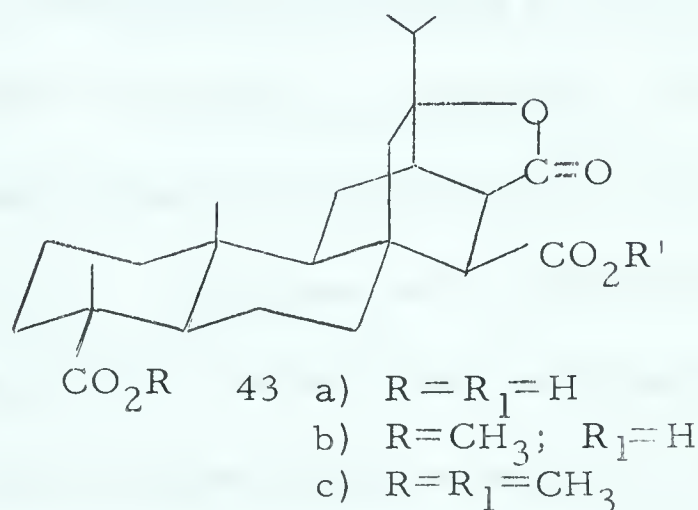
Maleopimaric acid (28a), $C_{24}H_{32}O_5$, m.p. $227-8^{\circ}C$, was first isolated in 1932 from the Diels-Alder addition of maleic anhydride to abietic acid (27a) at elevated temperatures^{31,33}. Later, the same adduct was found to result from a facile room temperature addition of maleic anhydride to levopimaric acid (26a)³⁴.

Since the mild conditions required for the addition to levopimaric acid preclude double bond rearrangement, it follows that the reactivity of abietic acid must result from a prior isomerization of the diene system to the cisoid arrangement possessed by levopimaric acid. Studies on the thermal isomerization of levopimaric acid to abietic acid have established the importance of a C-1 carboxy group in catalyzing this double bond migration, the rate being more than 50 times greater than that of the methyl ester 26b³⁵.

Although the gross structural features of maleopimaric acid are readily arrived at on the basis of the structure established for levopimaric acid, the stereochemical assignment is not as obvious and requires some comment. The arguments supporting structure 28a for maleopimaric acid can be summarized as follows.

If the α orientation of the C-13 hydrogen of levopimaric acid is taken as established^{27,28,29,30} then four isomeric adducts are theoretically possible. Employing the arguments of Lloyd and Hendrick³⁰,

the isolation of a single adduct indicates that the C-12 methyl inhibits formation of isomers deriving from β (topside) approach of maleic anhydride. Consequently, only two possibilities remain to be considered - the exo and endo isomers formed by approach of maleic anhydride from the less hindered α side of the diene system. Application of Alder's rule³⁶ then leads to the indicated structure (28a), a conclusion which is supported experimentally by the essentially quantitative conversion of maleopimaric acid to the lactone diacid 43a³⁷ with dilute aqueous hydrochloric acid³⁸, *.



Maleopimaric acid (28a), employed in the present studies, was initially obtained by the reaction of abietic acid with maleic anhydride following the procedure of Ruzicka et al³¹, or by refluxing a solution of rosin in p-cymene with an excess of maleic anhydride. In both preparations yields were in the order of 32-34%. Later investigations were facilitated when the adduct became commercially available and the laboratory preparation of maleopimaric acid was discontinued.

The infrared spectrum of maleopimaric acid showed the expected anhydride bands at 1849 cm^{-1} (m) and 1788 cm^{-1} (s)⁴¹, a strong

* For a discussion of the reliability of these arguments in determining the stereochemistry of Diels-Alder adduct see reference 39.

carboxyl carbonyl peak at 1702 cm^{-1} and weak absorption at 1643 cm^{-1} assigned to the olefinic bond.

Maleopimaric acid was readily converted with ethereal diazomethane to the corresponding methyl ester 28b, m.p. $214-15^{\circ}\text{C}$ (reported³¹ $214-15^{\circ}\text{C}$). When large quantities of the methyl ester were required it was found more convenient to convert maleopimaric acid to the acid chloride 31 (ν_{max} 1850 (m) , 1780 (s) , positive Beilstein test) with thionyl chloride in refluxing benzene followed by room temperature esterification with methanol in pyridine solution (overall yield $\simeq 65\%$). The C-1 carbomethoxyl group was identified by absorption at $\nu 1722\text{ cm}^{-1}$ and by a three proton signal at 6.33τ in the n.m.r. spectrum. The olefinic bond was characterized by weak infrared absorption at 1643 cm^{-1} and a one proton n.m.r. signal at 4.45τ . The presence of a succinic anhydride function was again established by the characteristic infrared doublet at 1849 cm^{-1} and 1782 cm^{-1} . The isopropyl group, located at 9.00τ , was identified by a characteristic splitting of 7 c.p.s.⁴² due to coupling with the C-18 hydrogen, and a three proton signal at 8.84τ , somewhat low for a saturated C-methyl group, was assigned to the C-16 methyl group because of the known deshielding effect of a β carbomethoxyl group⁴³.

On the basis of the above assignment the three proton signal at 9.41τ must be due to the angular methyl at C-12. This unusually high value for a C-methyl signal is undoubtedly due to the shielding by the C-7,8 olefinic bond since it is the only magnetically anisotropic group sufficiently close ($< 3\text{\AA}$ ⁴⁴) to exert such an effect.

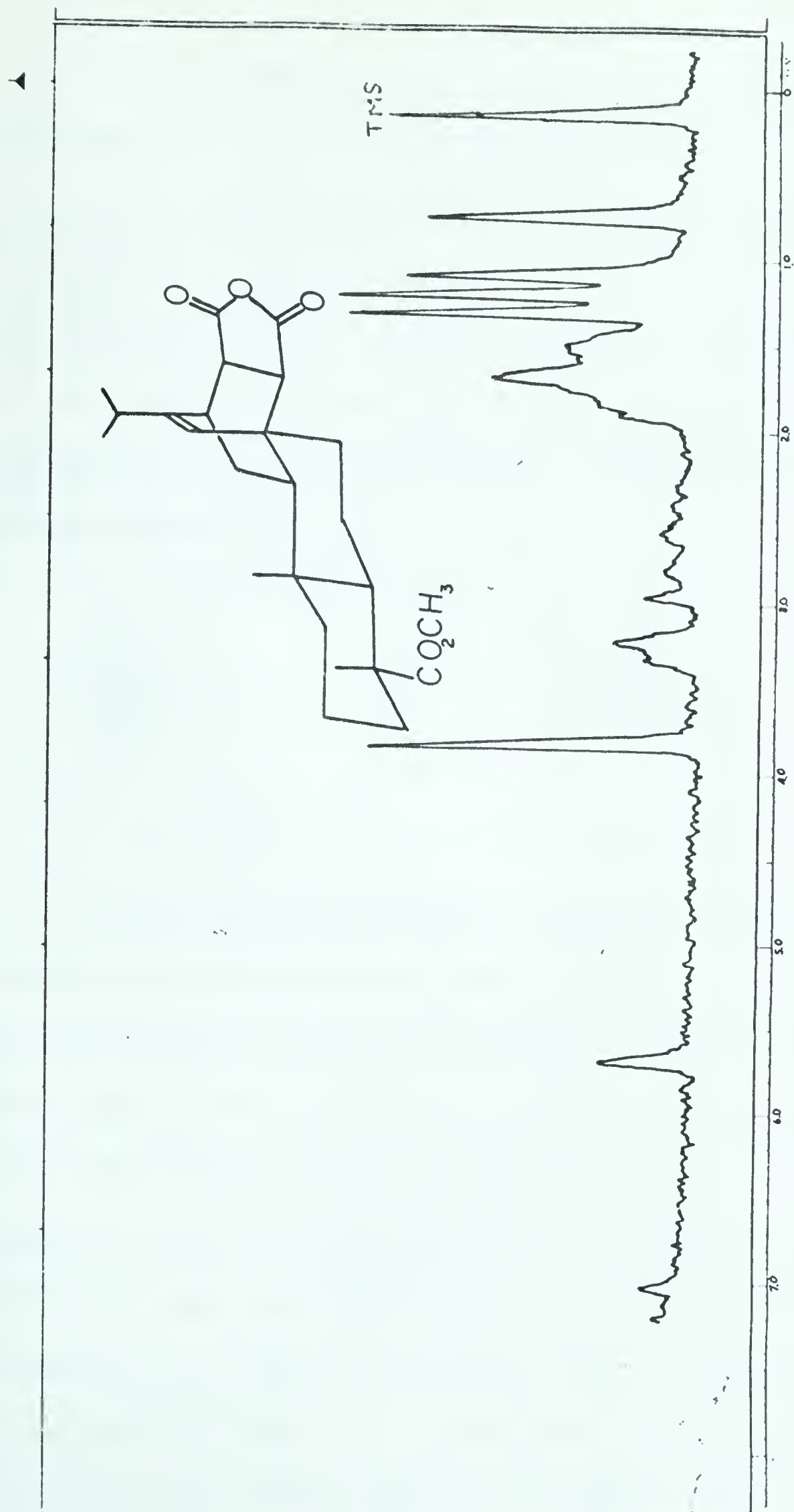
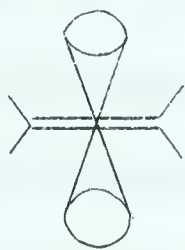
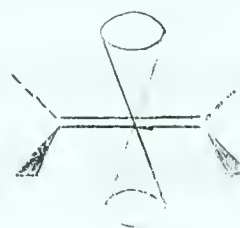


Figure 1. Nuclear magnetic resonance spectrum of methylmaleopimarate(28b).

The shielding area of an ethylenic bond is considered to be identical with that of a carbonyl group⁴⁵ and therefore can be described by a cone with an apical angle of $54^{\circ}44'$ whose axis is centered midway along the double bond and is orthogonal to it⁴⁶. At the time that these initial investigations were in progress the question as to whether the axis of this shielding cone was in the trigonal plane (structure I) or orthogonal to it as is the case for carbonyl compounds (structure II) was still being disputed^{45,47}.



Structure I



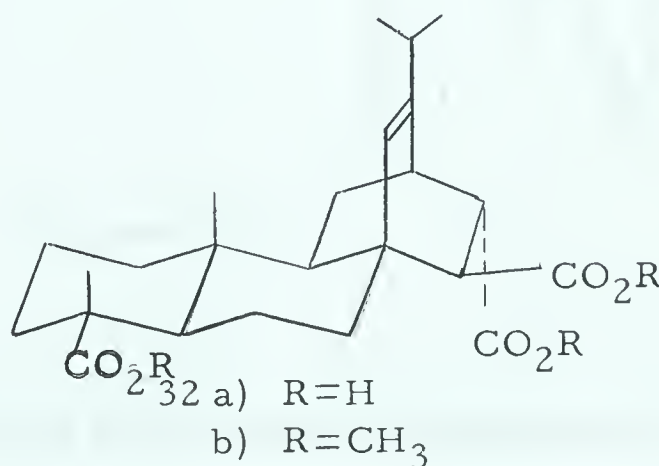
Structure II

Examination of the structure assigned to methyl maleopimarate (28b) clearly shows that shielding of the C-17 protons by the $\triangle^{7,8}$ olefinic bond is only possible if the latter case holds, that is if the axis of the shielding cone is orthogonal to the plane described by carbons 6, 7, and 8. Moreover, this anisotropy effect provides good evidence for a C-13 $\propto$ hydrogen in maleopimaric acid and hence also levopimaric acid because the alternative trans-syn backbone would increase the distance between the two groups to a point where shielding by the olefinic bond becomes negligible. This conclusion provides n.m.r. confirmation for a trans-anti ring fusion in levopimaric acid recently assigned on the basis of other evidence²⁷⁻³⁰. Further proof of the n.m.r. assignment is provided in the sequel.

II. STUDIES DIRECTED TOWARDS REMOVAL OF THE ANHYDRIDE GROUP OF MALEOPIMARIC ACID.

(a) Preparation of Fumaropimaric Acid (31a) and an Unsuccessful Attempt to Remove the C-21 and C-22 Carboxyl Groups with Lead Tetraacetate.

Maleopimaric acid was easily hydrolized to fumaropimaric acid (32a) $C_{24}H_{34}O_6 \cdot H_2O$, m.p. $193-5^{\circ}C$, ν_{max} 1710 cm^{-1} by brief refluxing with alcoholic potassium hydroxide. This transformation could be reversed by distilling fumaropimaric acid under vacuum at $250^{\circ}C$ onto a cold finger. Recrystallization of the solid distillate provided a sample of maleopimaric acid, m.p. $226-8^{\circ}C$, identified by comparison of its infrared spectrum with that of authentic material. An attempt to effect this conversion in refluxing acetic anhydride led only to an oily mixed anhydride (ν_{max} $1825, 1750\text{ cm}^{-1}$) from which fumaropimaric acid could be recovered by acid catalized hydrolysis.



A trans relationship of the C-21, C-22 carboxyl group was established by conversion to the oily trimethyl ester 32b with ethereal diazomethane (ν_{max} 1730 cm^{-1} , n.m.r. signals at 6.38, 6.31 and 6.27 τ).

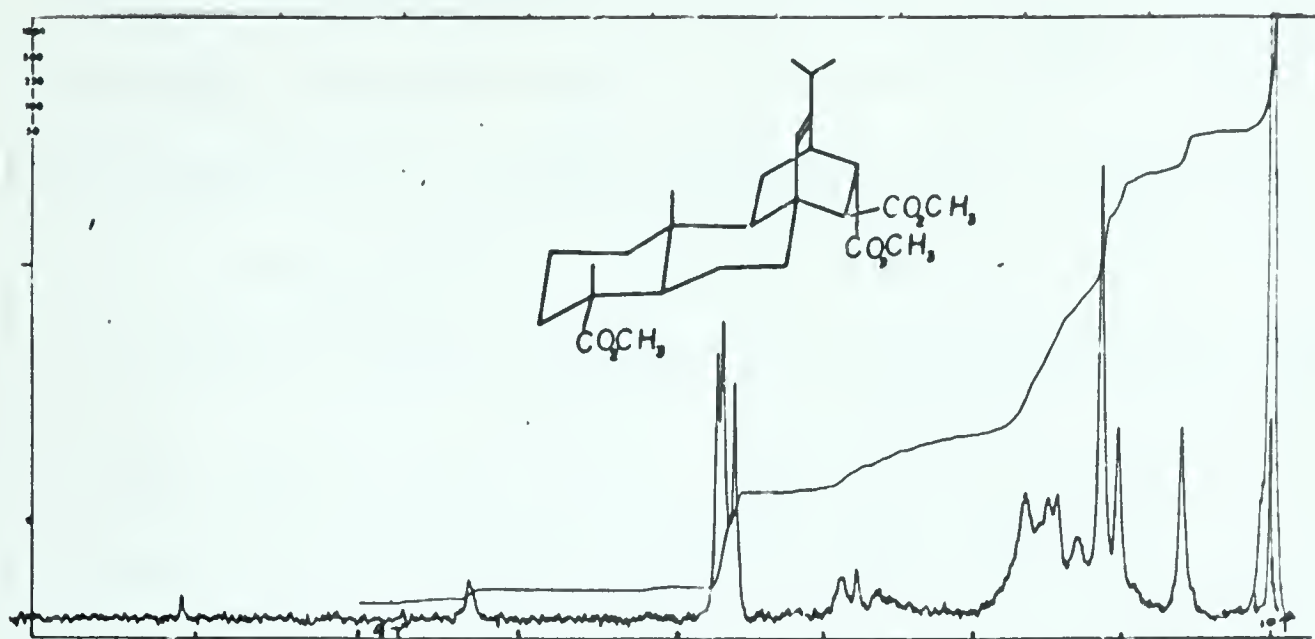


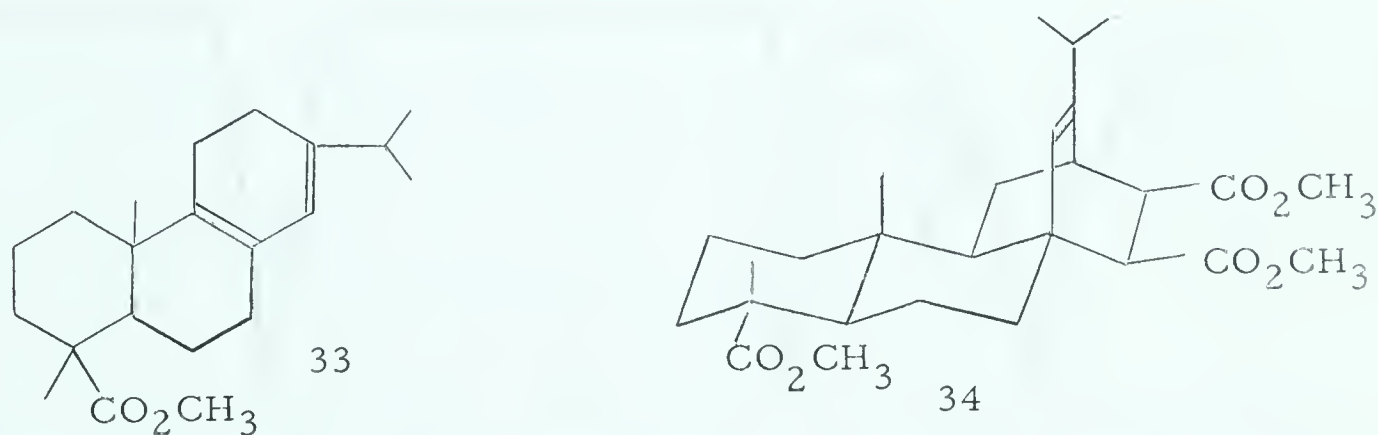
Figure 2. Nuclear magnetic resonance spectrum of trans trimethyl ester 32b.



Figure 3. Infrared spectrum of the trans trimethyl ester 32b.

Vacuum distillation of the trimethyl ester 32b at 270°C yielded a solid distillate, which after purification, was identified as dimethyl fumarate by melting point, mixture melting point and infrared spectral comparison with authentic material. The undistilled oil exhibited ultraviolet absorption at 265 $m\mu$ probably due to the presence of methyl palustrate (33) ($\lambda_{\max}$ 266 $m\mu$) known to be an intermediate in the thermal isomerization of methyl levopimarate to methyl abietate⁴⁸.

Supporting evidence for a trans configuration of the C-21, C-22 carbomethoxyl functions was obtained by the preparation of authentic cis trimethyl ester 34, $C_{27}H_{40}O_6$, m.p. 103-05°C (reported⁴⁹ 103°C) from maleopimaric acid by the silver salt-methyl iodide esterification procedure described by Ruzicka, Ankersmit and Frank (reference 31). The eclipsed relationship of the C-21, C-22 carbomethoxyl groups was established by



heating a sample under vacuum at 300°C. The oily distillate obtained was identified as dimethyl maleate by comparison of its infrared spectrum and refractive index ($n_D^{19.9}$ 1.45; reported, 1.44) with authentic material. Comparison of the infrared spectrum of the cis trimethyl ester 34 with the oily trimethyl ester 32b clearly indicated that the two compounds were not identical and consequently supported a trans arrangement of the C-21,

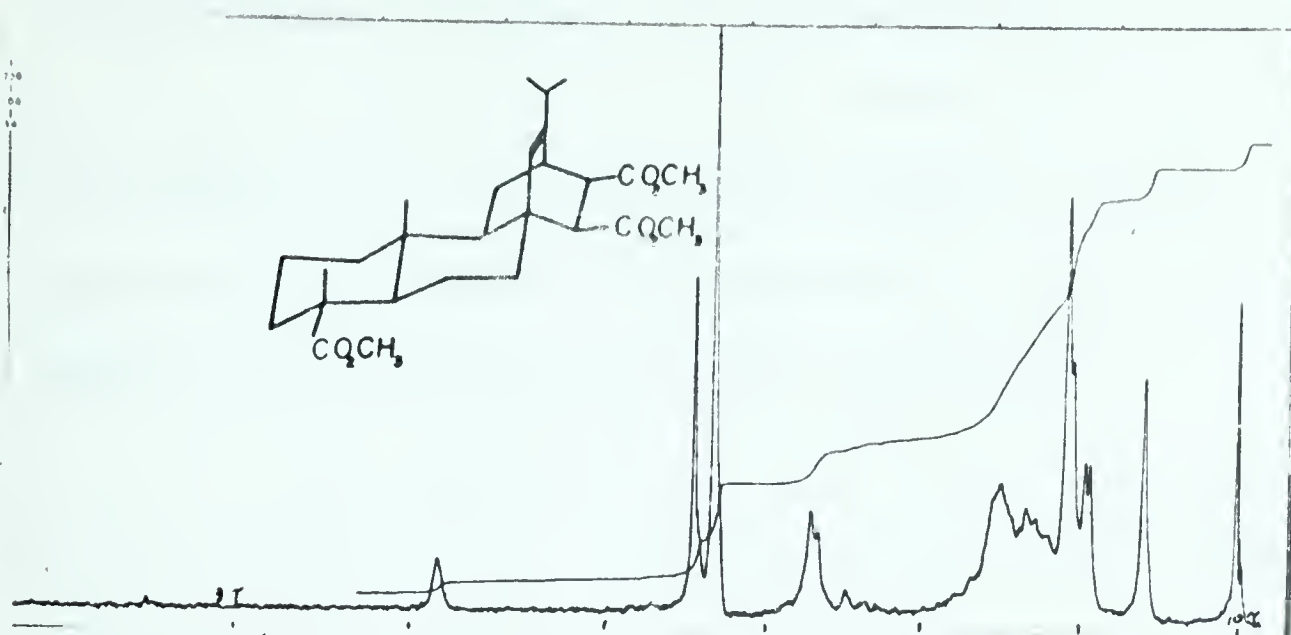


Figure 61. Nuclear magnetic resonance spectrum of the cis trimethyl ester 34.

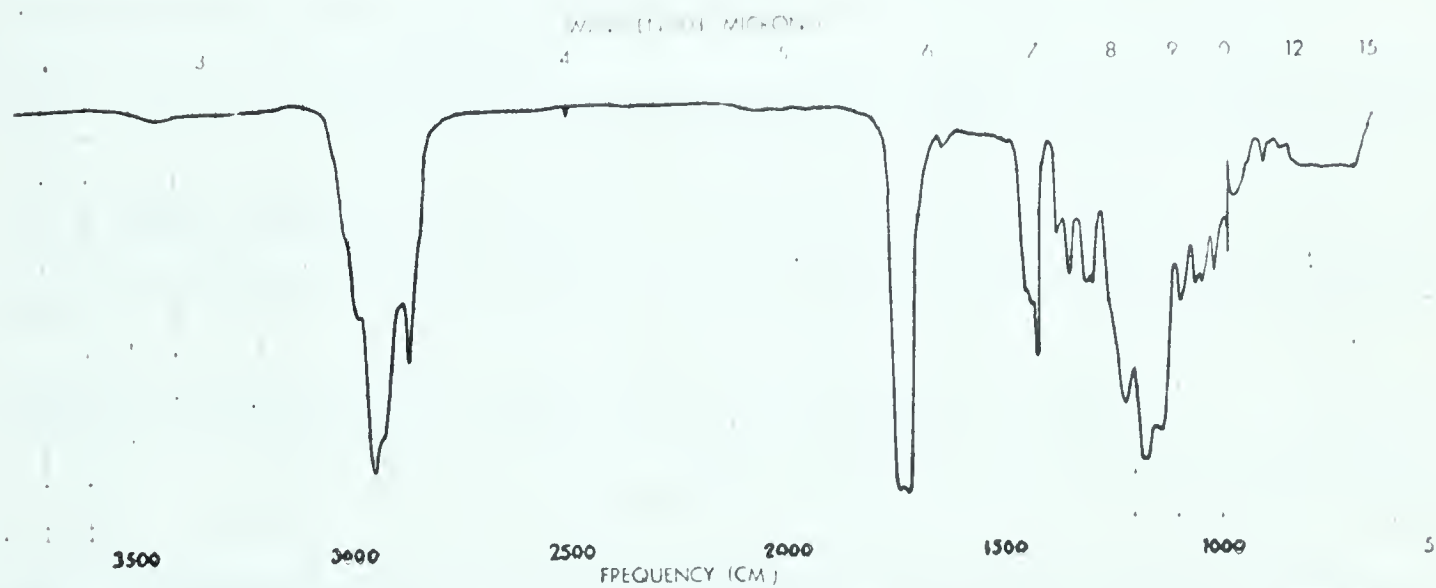


Figure 62. Infrared spectrum of the cis trimethyl ester 34.

C-22 carbomethoxyl groups in the latter compound.

Further confirmation for the trans relationship was provided by the Diels-Alder reaction of rosin with fumaric acid⁵⁰. The adduct obtained was identical with the triacid 32a by melting point, mixture melting point and infrared spectral comparison.

The assumption that a C-21 endo carboxyl is destabilized by non-bonded interaction with the isopropyl methyls permits the assignment of an exo configuration to the C-21 carboxyl in fumaropimaric acid because the reversible nature of the Diels-Alder reaction would lead to formation of the thermodynamically more stable configuration.

The same argument also holds for the epimerization of the cis trimethyl ester 34 to the trans trimethyl ester 32b with potassium methoxide in methanol (characterization by infrared spectral analysis). The reversible nature of this equilibration leads to the assignment of a C-21 exo carbomethoxyl group in 32 b if the assumption is again made that the important destabilizing force is a non-bonded interaction between the isopropyl group and an endo C-21 carbomethoxy group[‡].

Conversion of the cis trimethyl ester 34 to the trans ester 32b was accompanied by some characteristic changes in the infrared and n.m.r. spectra which are now described since they will be of value in establishing the configuration of C-21 carboxyl or carbomethoxyl groups in compounds to be discussed later.

[‡] Recently the assignment of a C-21 exo carboxyl group in fumaropimaric acid has been made from other evidence (reference 51).

The C-21 endo carbomethoxyl group of the cis triester 34 was identified by infrared absorption at 1749 cm^{-1} and 1730 cm^{-1} and by n.m.r. signals at 6.47τ (6H) and 6.33τ (3H). In the C-21 exo epimer (32b) only one infrared band was present ($\nu_{\text{max}} 1730\text{ cm}^{-1}$) while the n.m.r. spectrum now contained three carbomethoxyl signals, all at lower field (6.38 , 6.31 , and 6.27τ) than observed for the endo epimer.

In the cis trimethyl ester 34 the six proton signal at 6.47τ is assigned to the C-21 and C-22 carbomethoxyl groups, their relatively high field position being explained in terms of shielding contributions from the $\Delta^{7,8}$ olefinic bond and the eclipsing ester group. In the trans triester 32b, the C-21 carbomethoxyl group is no longer shielded by either the olefinic bond or the adjacent function and therefore is assigned to the low field signal at 6.27τ . The C-22 carbomethoxyl group, however, occupies an intermediate position since it still lies within the shielding cone of the olefinic bond. The slightly shielded position of the high field signal (6.38τ) is for this reason assigned to the C-22 carbomethoxy group.

The cause of the high ester carbonyl absorption ($\nu_{\text{max}} 1749\text{ cm}^{-1}$) in the cis trimethyl ester 34 is unclear, yet its occurrence in this and other compounds for which eclipsed carbomethoxyl groups are postulated, give it an empirical utility in identifying this structural unit.

Earlier attempts to hydrolyze the anhydride function under mild, presumably non-epimerizing conditions (aqueous acetone and aqueous pyridine) were unsuccessful because of the known tendency of eclipsed carboxyl groups to exist as the anhydride^{52,53}. More precise

indication of the resistance of maleopimaric acid to undergo hydrolysis was obtained by dissolving it in aqueous base followed by acidification with dilute hydrochloric acid. Esterification of the crude product with ethereal diazomethane and chromatography on alumina provided equal amounts (ca. 30%) of the cis trimethyl ester 34 and methyl maleopimarate 28b. Isolation of the trimethyl ester 34 is taken as proof for the presence of an equal amount of the corresponding triacid in the crude hydrolysis product [‡].

In a control experiment the hydrolysis product prepared as above, was dried under vacuum at 155°C for two hours, then esterified and chromatographed on alumina. No cis trimethyl ester 34 was detected, the only product being the anhydride 28b. In both experiments, the failure to achieve a material balance was traced to the tendency of the anhydride function to react with the alumina. Thus chromatography of methyl maleopimarate (28b) on acidic, basic and neutral alumina as well as on Florisil resulted in all cases in extensive tailing and incomplete recovery of sample.

It seemed reasonable to assume that the epimerization encountered in aqueous alcohol solution was being preceded by an alcoholysis step since the anhydride ring of maleopimaric acid is known to be susceptible to cleavage by ethanol⁵⁵ and also because esters have been found to be more readily epimerized by base than the corresponding carboxylic acids⁵⁶.

[‡] Subsequent to the completion of this work there appeared an account⁵⁴ of similar difficulties encountered in an attempted hydrolysis of maleopimaric acid with aqueous acetone and aqueous sodium hydroxide.

Support for this view was obtained from two experiments with maleopimaric acid which differed only in that one involved an initial mild hydrolysis of the anhydride ring with dilute aqueous base whereas in the second experiment this step was replaced by brief refluxing in methanol. The two solutions were then made identical by addition of appropriate amounts of methanol to the first and aqueous base to the second and, after a period of refluxing, each was acidified with dilute aqueous hydrochloric acid, the products dried under vacuum at 150°C for 90 minutes, esterified and chromatographed on neutral alumina. From the hydrolysis reaction only methyl maleopimarate (28b) was isolated (45% yield), whereas under methanolysis conditions approximately equal amounts (~30%) of the anhydride (28b) and the trans trimethyl ester 32b were obtained.

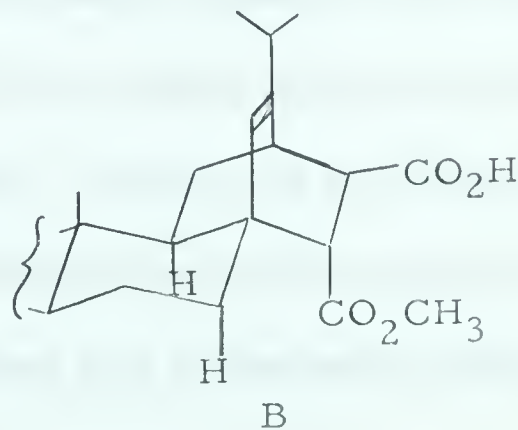
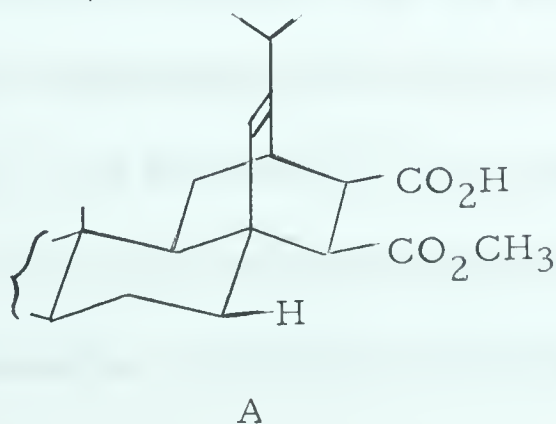
The sequence of events in the first experiment is considered to involve an initial hydrolysis of the anhydride ring with sodium hydroxide resulting in formation of the tri- (or more likely di-)† sodium salt where the C-21 and C-22 carboxyl groups are, and remain in an eclipsed configuration during the subsequent period of refluxing with sodium hydroxide in aqueous methanol. Acidification with aqueous hydrochloric acid then yields a mixture of maleopimaric acid and the cis triacid which is reconverted to the anhydride by heating under vacuum at 150°C.

† pK_{*MCS} determination has given values of 7.61 and 8.98 for two of the carboxyl groups of maleopimaric acid; the pK_{*MCS} of the third carboxyl group was too high to be measured. (Private communication from Dr. W. Simon, Eidg. Technische Hochschule, Zurich)

In the second experiment the anhydride ring is at least partially cleaved to the monomethyl ester by the initial period of refluxing in methanol and by a subsequent attack of methoxide following the addition of aqueous sodium hydroxide. In order to explain the apparent restriction of epimerization to a C-21 carbomethoxyl group it is necessary to assume that if any of the C-22 monomethyl ester is formed it is hydrolyzed directly to the cis triacid while the C-21 ester is capable of undergoing a competitive epimerization leading to formation of a C-21 exo methyl ester and following hydrolysis, to fumaropimaric acid.

One possible explanation for the reluctance of a C-22 carbomethoxyl group to undergo epimerization can be found in the observation that the ease of proton abstraction is hindered by axial protons at C-5 and C-9 causing the ratio $k_{\text{hyd.}}/k_{\text{epim.}}$ to approach infinity. In the case of a C-21 carbomethoxyl group, where only one such 1,3 diaxial interaction exists, it is assumed that proton abstraction is more likely to occur with the result that $k_{\text{hyd.}}/k_{\text{epim.}}$ now becomes finite.

Alternatively, it can be argued that epimerization of the C-22 carbomethoxyl group does not occur because the eclipsed form (part structure A) is thermodynamically more stable than the C-22 exo epimer (structure B).



Inspection of molecular models shows that the eclipsed configuration is destabilized by non-bonded interactions between the C-21 carboxyl and C-22 carbomethoxyl groups, as well as between this latter group and the equatorial hydrogen at C-9. In the exo epimer, the main destabilizing contributions are from two 1,3 diaxial interactions of the type just mentioned (with the axial hydrogens at C-13 and C-9) and from eclipsed hydrogen-carbomethoxyl and hydrogen-carboxyl interactions.

From the value of ΔF obtained for the epimerization of an axial carboethoxyl to an equatorial configuration in a cyclohexane ring (1.2-1.4 kcal.)¹⁰⁹, a value of 0.6 kcal. is assigned to each of the 1,3 diaxial H, CO₂CH₃ interactions present in the systems now under discussion.

An approximation of the extent of stabilization realized in altering the fully opposed configuration of the C-21 and C-22 substituents in structure A to the less serious opposed arrangement of structure B can be found in the values assigned for the analogous situation in n-butane (0.9-2.6 kcal.)¹¹⁰. Although the steric requirements of the carbomethoxyl and carboxyl group cannot be estimated accurately, especially because of the possibility of solvation in the latter case, it does not appear unreasonable to assume that the energy difference between these two possible configurations (structures A and B) probably lies between 0.0 and 1.4 kcal.. It can therefore be argued that, considering non-bonded interactions alone, the eclipsed epimer is probably less stable than the C-22 exo alternative. However, if the possibility of a preferential hydrogen

bonding between the carboxyl and an eclipsed carbomethoxyl group is allowed for, then this conclusion might well be invalidated. In this event, the failure of a C-22 carbomethoxyl group to epimerize would have to be attributed to the fact that the fully eclipsed form is thermodynamically more stable than the alternative configuration (structure B).

Initial attempts to remove the C-21 and C-22 carboxyl groups of fumaropimaric acid with lead tetraacetate were hampered by its low solubility in acetonitrile and other solvents in use at that time, and, as it was later discovered, by the multiplicity of products derivable from this system. As a result, efforts to isolate reaction products either by recrystallization or by esterification and chromatography were unsuccessful. Further studies were therefore temporarily abandoned and attention turned to modifying the carboxyl group at C-1 with a view to applying the Hunsdieker reaction. The two methods which were developed for this purpose are now described.

(b) Preparation of the Hydroxy Anhydride 35.

This initial approach was suggested by the report that acid anhydrides show only a small amount of reduction on prolonged heating with sodium borohydride and consequently permit the selective reduction of more reactive groups such as acid chlorides, in compounds containing both functional groups⁵⁷.

Slow addition of a 0.8 molar solution of sodium borohydride in diglyme to the acid chloride 31 in diglyme with vigorous stirring

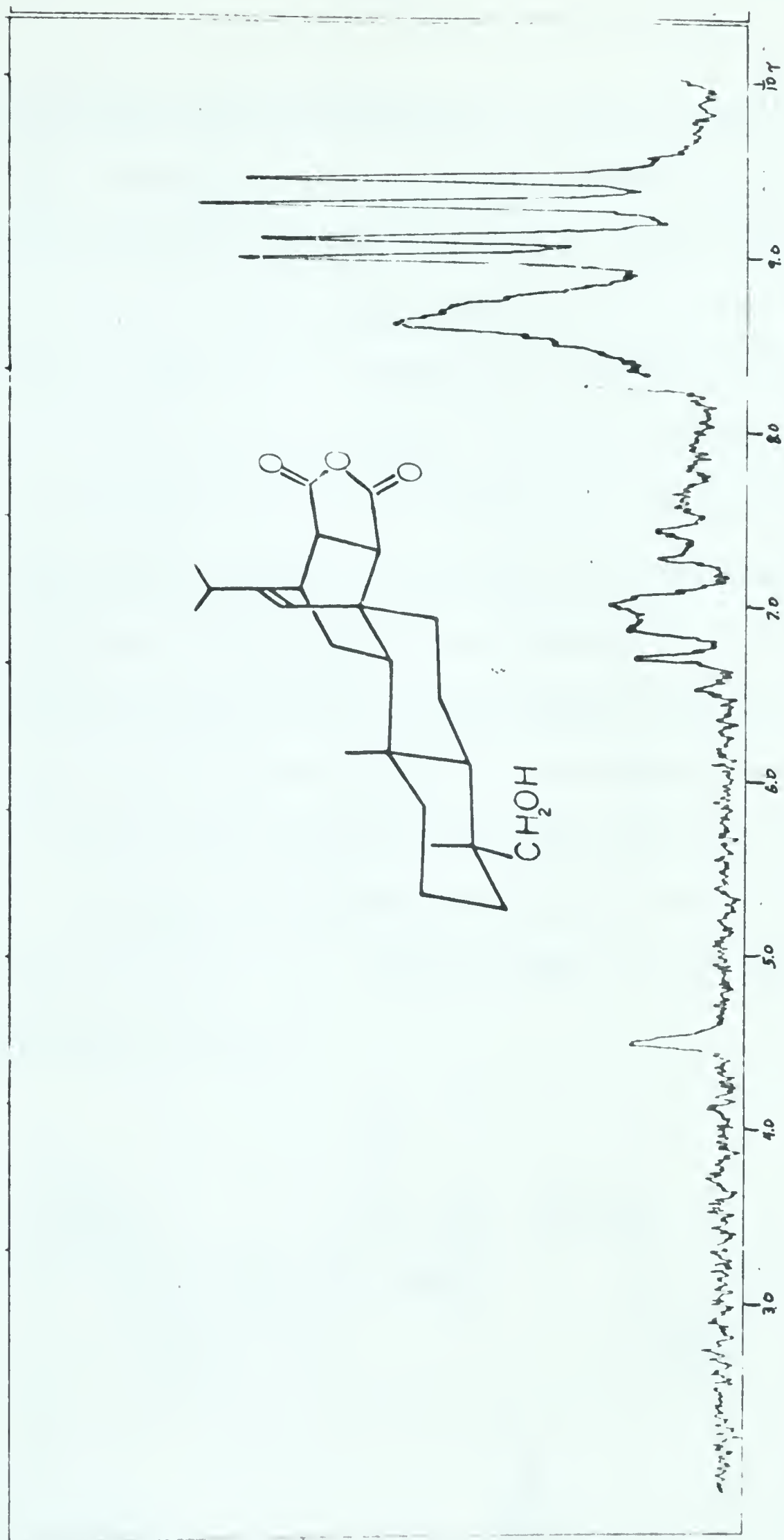
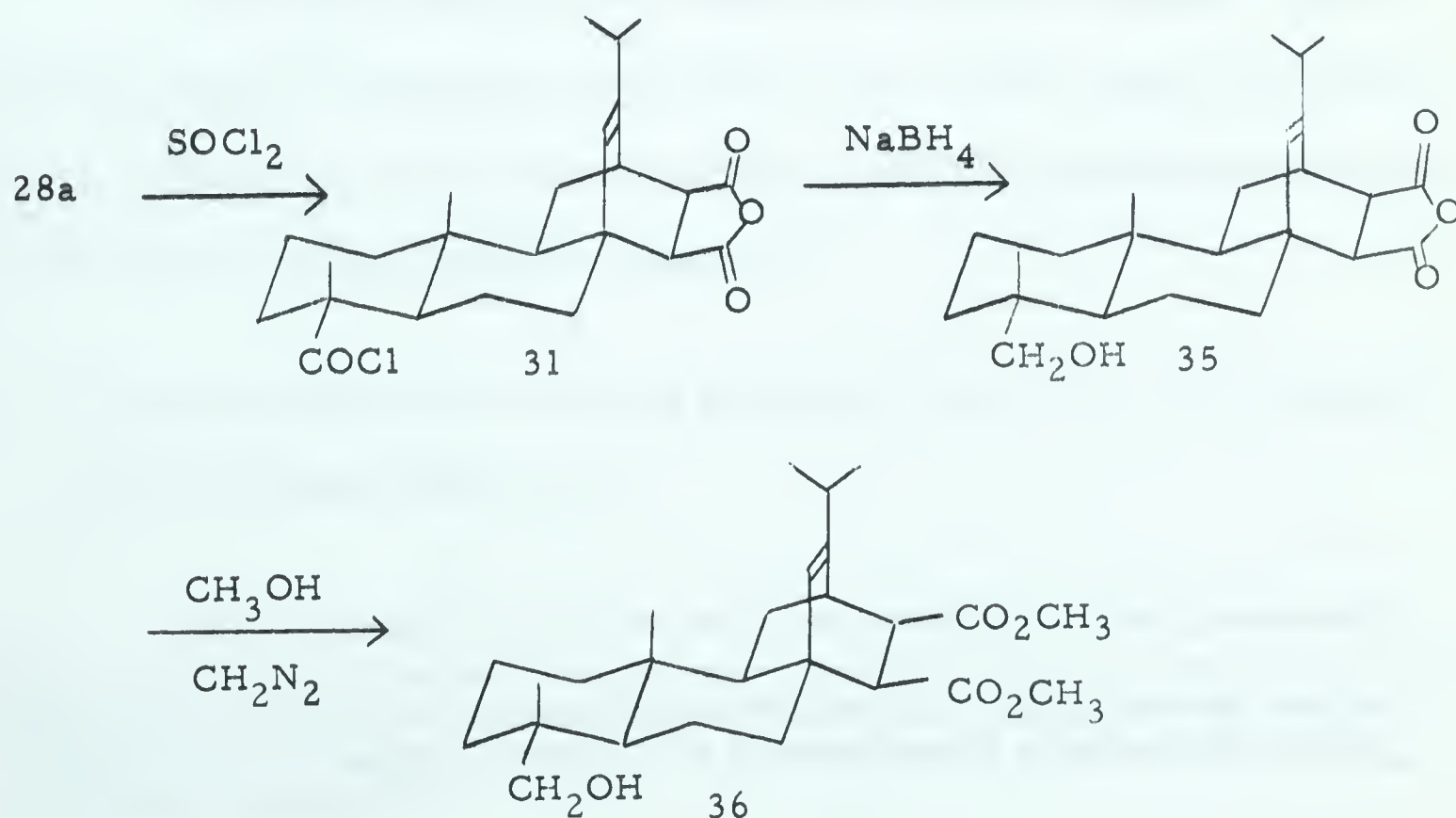
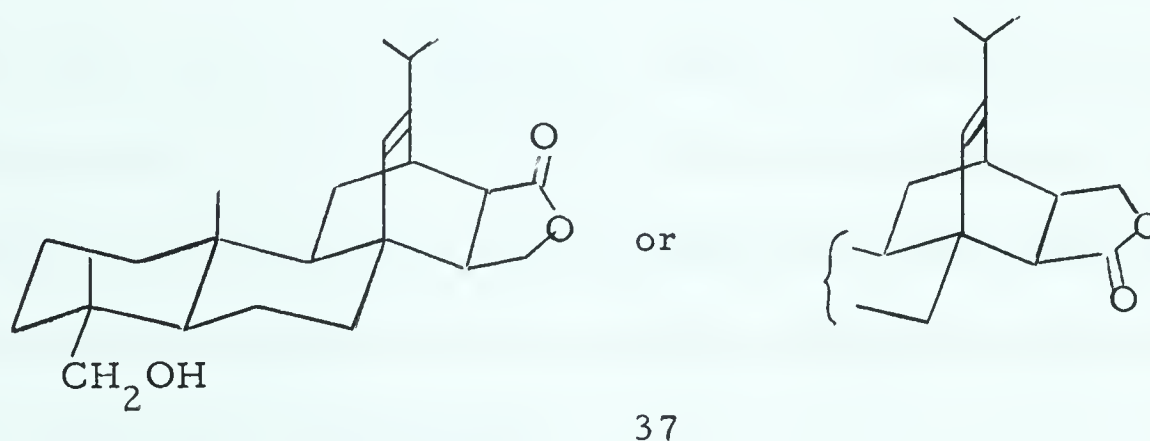


Figure 4. Nuclear magnetic resonance spectrum of the hydroxymethyl anhydride 35.

provided the desired hydroxy anhydride 35, $C_{24}H_{34}O_4$, m.p. 151-53°C in 9% yield. The presence of hydroxyl and anhydride groups were established by infrared absorption at 3630 cm^{-1} (sharp), 1848 cm^{-1} (m) and 1782 cm^{-1} (s). The C-1 axial methyl was found to have moved upfield from its position at ca. 8.85τ in C-1 carbomethoxy derivatives to 9.24τ in the hydroxy anhydride 35. This shift is almost 0.2 p.p.m. greater than expected on the basis of inductive effects alone and may reflect a diamagnetic shielding contribution from the hydroxyl group. The hydroxy anhydride 35 was further characterized by conversion with methanolic diazomethane to the dimethyl ester 36, $C_{26}H_{40}O_5$, m.p. 148-50°C. The C-1 hydroxymethyl group was identified by infrared absorption at 3640 cm^{-1} (sharp) and by the high field position of the C-16 axial methyl (9.24τ). The endo carbomethoxyl groups at C-21 and C-22 were characterized by a 6 proton n.m.r. signal at 6.43τ and a strong infrared absorption band at 1745 cm^{-1} ,



In an earlier experiment, the acid chloride 31 was added to an excess of sodium borohydride in diglyme and the solution stirred at 85°C. Under these conditions the anhydride ring was also attacked, resulting in formation of the hydroxy lactone 37, $C_{24}H_{36}O_3$, m.p. 172-76°C. The C-1 hydroxymethyl group was identified by infrared absorption at 3610 cm^{-1} and 3475 cm^{-1} and by the C-1 axial methyl signal at 9.24τ in the n.m.r. spectrum. The presence of a γ lactone was deduced from a strong infrared absorption band at 1759 cm^{-1} . No attempt was made to determine whether the C-21 or the C-22 carboxyl had undergone reduction and consequently this aspect of the structure remains in doubt.



The wide melting point range of the purified sample, together with the presence of satellite peaks ($J = 7\text{ c.p.s.}$) on the isopropyl doublet, suggests that it may still contain a small amount of contaminating material, possibly the alternate lactone or a lactol[‡].

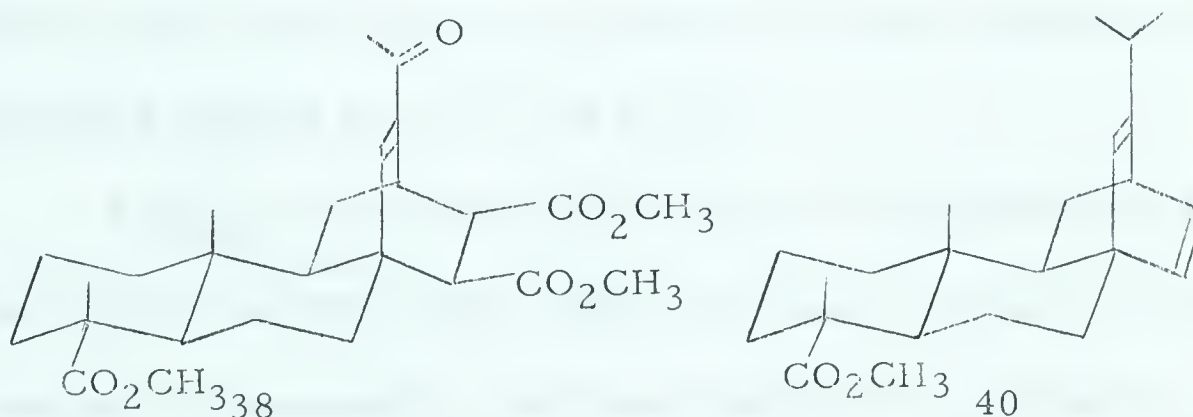
(c) Partial Saponification of the Cis Trimethyl Ester 34 and the Saturated Lactone Dimethyl Ester 43c.

Discouraged by the low yields encountered in the preparation

[‡] Since the completion of this work a reduction of the anhydride ring of a *Gibberella* metabolite, fujenol to a lactone-lactol mixture with $NaBH_4$ has been reported⁵⁹.

of the hydroxy anhydride 35, attention was next turned to the preparation of maleopimaric acid derivatives containing a C-1 carbomethoxyl function in the hope that they would provide a more convenient model on which to develop a method for removing the C-21 and C-22 carboxyl groups.

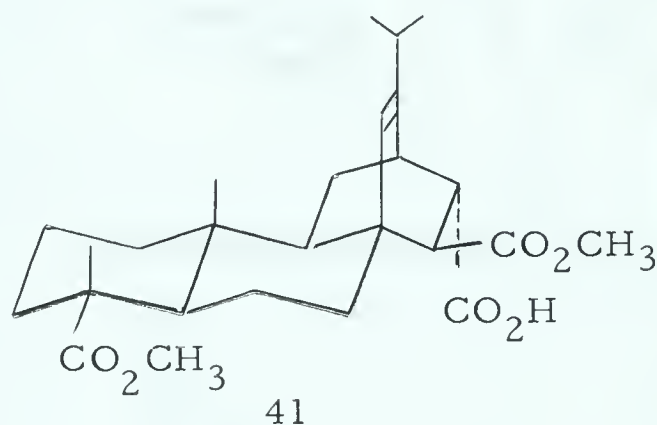
In 1940 Ruzicka and Kaufmann reported an oxidation with ozone of cis trimethyl ester 34 to the methyl ketone 38 which among other trans-formations was saponified to a monoacid 56a⁴⁹ (see page 62 of this thesis). Although these workers did not assign a structure to the monoacid it appeared reasonable that, because of the mild reaction conditions, saponification would involve either the C-21 or the C-22 carbomethoxyl groups rather than the hindered C-15 ester. An extension of this reaction to the cis trimethyl ester 34 itself seemed desirable since a successful Hunsdieker decarboxylation would provide a β bromo ester which, on saponification, hopefully could be made to undergo a second decarboxylation to the bicyclo octadiene 40.



Rather than employ the tedious and expensive silver salt-methyl iodide process reported by Ruzicka and co-workers^{31,49}, two alternative methods for preparing the trimethyl ester 34 were developed. One, involving the esterification of a methanolic solution of maleopimaric acid

with diazomethane, was more convenient for small scale preparations while the second, which involved refluxing the acid chloride 31 in anhydrous methanol, was preferable when larger quantities (100-200 g.) of the trimethyl ester were required.

Utilizing the procedure employed in saponifying the methyl ketone 38⁴⁹, the trimethyl ester 34 was converted without difficulty to the monoacid 41, $C_{26}H_{38}O_6$, m.p. 183-86°C. The presence of a carboxyl



group was shown by broad infrared absorption between 3400 and 2500 cm^{-1} and by carbonyl peaks at 1730 cm^{-1} and 1705 cm^{-1} , the lower one presumably being due to the carboxyl function. Further support for a monoacid formulation came from the n.m.r. spectrum which contained 3-proton carbomethoxyl signals at 6.30 τ and 6.37 τ .

A trans orientation of the C-21 and C-22 substituents follows from the thermal decomposition of the monoacid 41 which provided a small amount of monomethyl fumarate identified by comparison of its melting point (143-45°C, reported 144°C) and infrared spectrum with that of authentic material. This conclusion is supported and extended by the observation that the monoacid 41 is converted with diazomethane to the oily trans trimethyl ester 32b. On the strength of arguments already

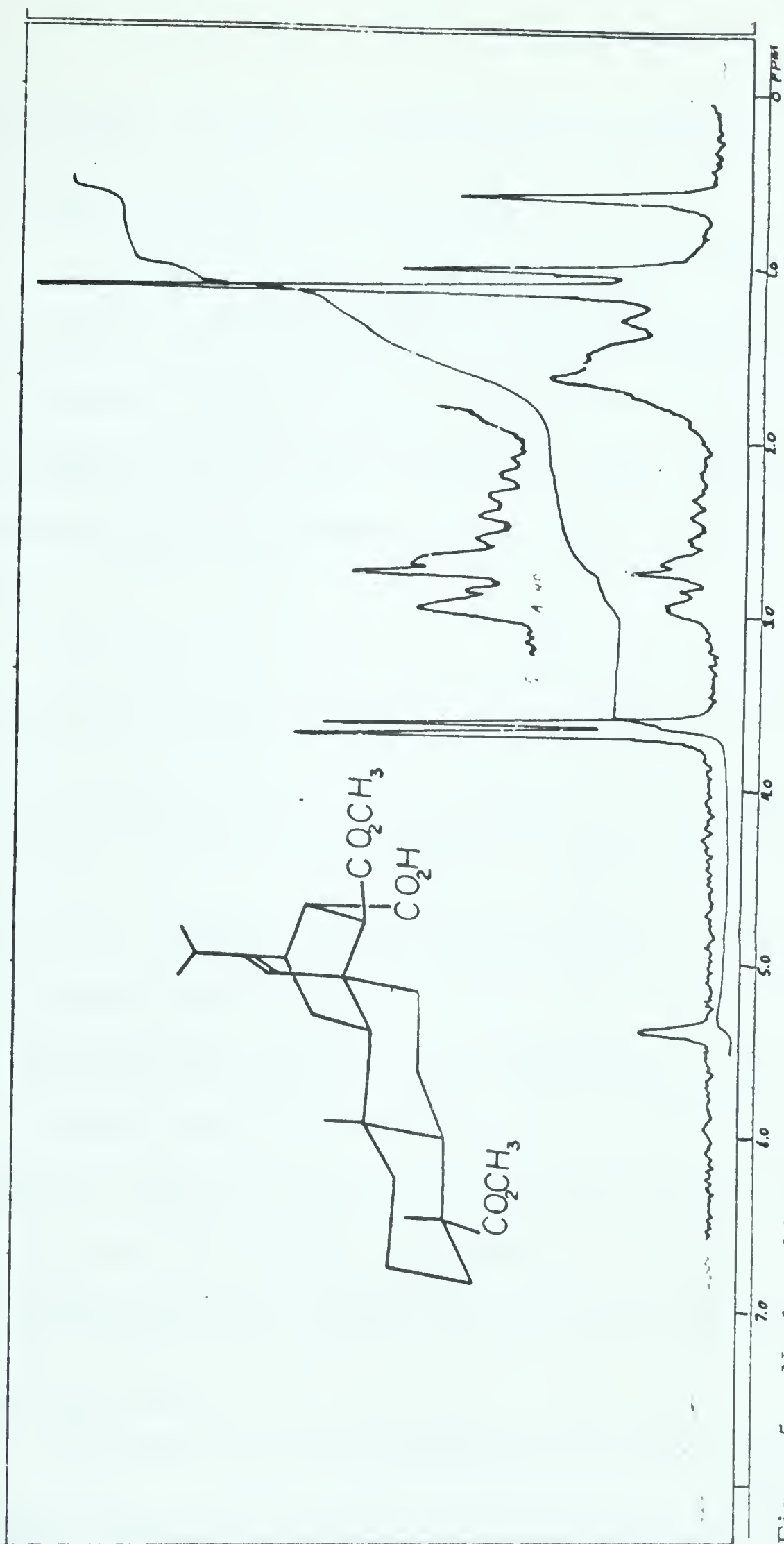


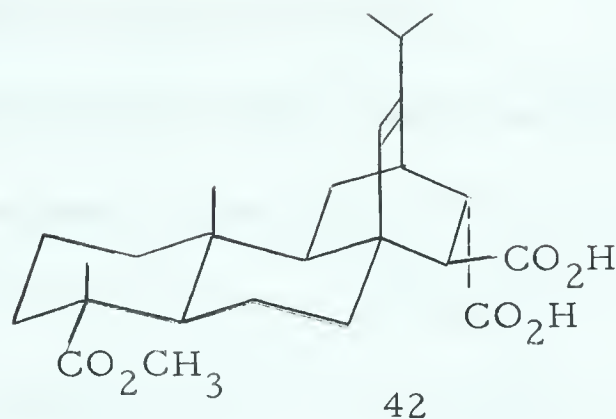
Figure 5. Nuclear Magnetic resonance spectrum of the monoacid 41.

presented (page 19), this correlation therefore permits the assignment of a C-21 exo substituent in the monoacid 41.

A comparison of the carbomethoxyl region with that of the trans trimethyl ester 32b ($\gamma=6.38, 6.31$ and 6.27) clearly showed that the low field signal was absent in the monoacid 41. Since this peak has been assigned to the C-21 exo carbomethoxyl group (see page 20), it must therefore have undergone saponification during formation of the monoacid 41.

The failure to observe any epimerization of the C-22 carbomethoxyl group can be attributed, as in previous cases, to both kinetic and thermodynamic factors. Thus, although the C-22 exo epimer is probably more stable than the eclipsed configuration in the absence of intramolecular hydrogen bonding (see page 24), its formation would appear less favoured than epimerization at C-21 which removes a 1,3 quasi axial interaction with the C-7 isopropyl group. From a kinetic point of view the preferential epimerization of a C-21 carbomethoxyl substituent is anticipated because proton abstraction and hence enolization should be more readily accomplished at C-21 than at C-22. The subsequent saponification of this group is not unexpected in view of its exposed α position.

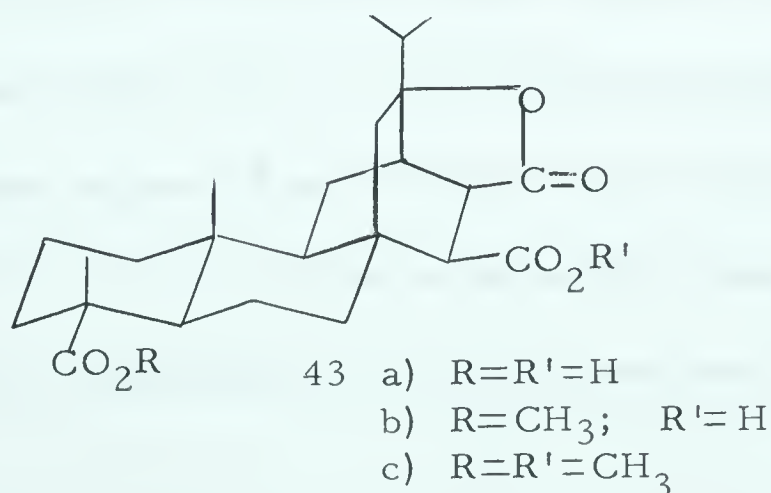
Saponification of the cis trimethyl ester 34 under more vigorous conditions (refluxing for 45 minutes with 10% sodium hydroxide in aqueous-methanol) provided the diacid, methyl fumaropimarate (42), $C_{25}H_{36}O_6$, m.p. $274-79^{\circ}C$ in 40% yield.



The carboxyl groups were identified by infrared absorption at 3200 cm^{-1} and a strong band at 1705 cm^{-1} and the ester function by carbonyl absorption at 1725 cm^{-1} .

The diacid 42 was also obtained by the Diels-Alder addition of fumaric acid to impure methyl abietate (corrected yield = 26%) and in a 25% yield by the hydrolysis of methyl maleopimarate 28b with sodium hydroxide in aqueous methanol. The identity of the three preparations was established by melting point, mixture melting point and infrared spectral comparison. As expected, esterification with diazomethane provided the trans trimethyl ester 32b which was identified by its infrared spectrum.

The final compound to be prepared in connection with these studies was the lactone monoacid 43b, $\text{C}_{25}\text{H}_{36}\text{O}_6$, available from the



corresponding dimethyl ester in 84% yield by mild saponification with sodium hydroxide in aqueous dioxane.

The synthetic utility of the lactone acid 43b lay in the fact that a reaction sequence analogous to that projected for the monoacid 41 would place a hydroxyl group at C-7 thereby providing a means for removing the isopropyl group via dehydration to the isopropylidene derivative.

Spectral confirmation for the formulation of 43b as a mono acid was found in broad infrared absorption between 2400 and 3400 cm^{-1} and in a single 3 proton carbomethoxyl signal at 6.33 τ . The decision in favor of a C-22 carboxyl group is based first on the expected resistance of the C-15 carbomethoxyl group to saponification under the mild reaction conditions employed and secondly on a comparison of the infrared spectra of the starting material (43c) and product (43b). Reference has already been made to the fact that eclipsed carbomethoxyl functions at C-21 and C-22 give rise to a distinct infrared absorption band at a higher frequency than the C-15 carbomethoxyl group. In the compounds discussed thus far, the C-15 ester absorption was found to range between 1722 cm^{-1} and 1730 cm^{-1} , while in the two compounds containing endo C-21 and C-22 carbomethoxyl groups (34 and 36) the high frequency absorption was located at 1749 cm^{-1} and 1745 cm^{-1} . In the lactone dimethyl ester 43c the ester carbonyl bands appeared at 1745 cm^{-1} and 1730 cm^{-1} , while in the lactone monoacid 43b only the C-15 ester absorption was present (1732 cm^{-1}), there being no indication of a C-22 carbomethoxyl group either in the form

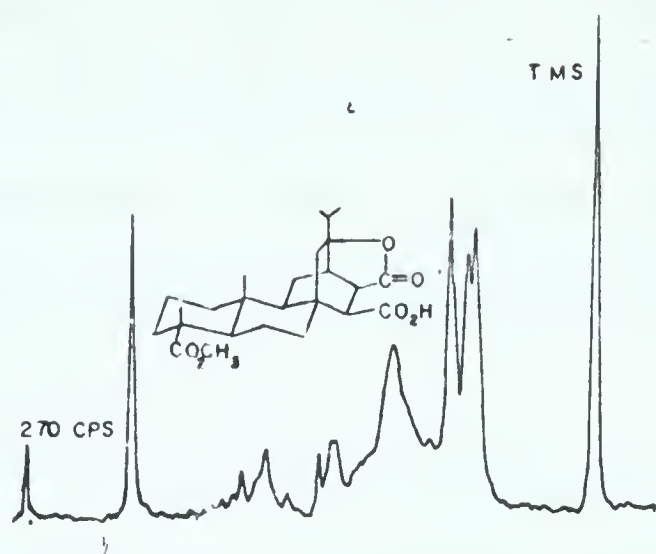


Figure 6. Nuclear magnetic resonance spectrum of the lactone monoacid 43b. at 60 mc/sec.

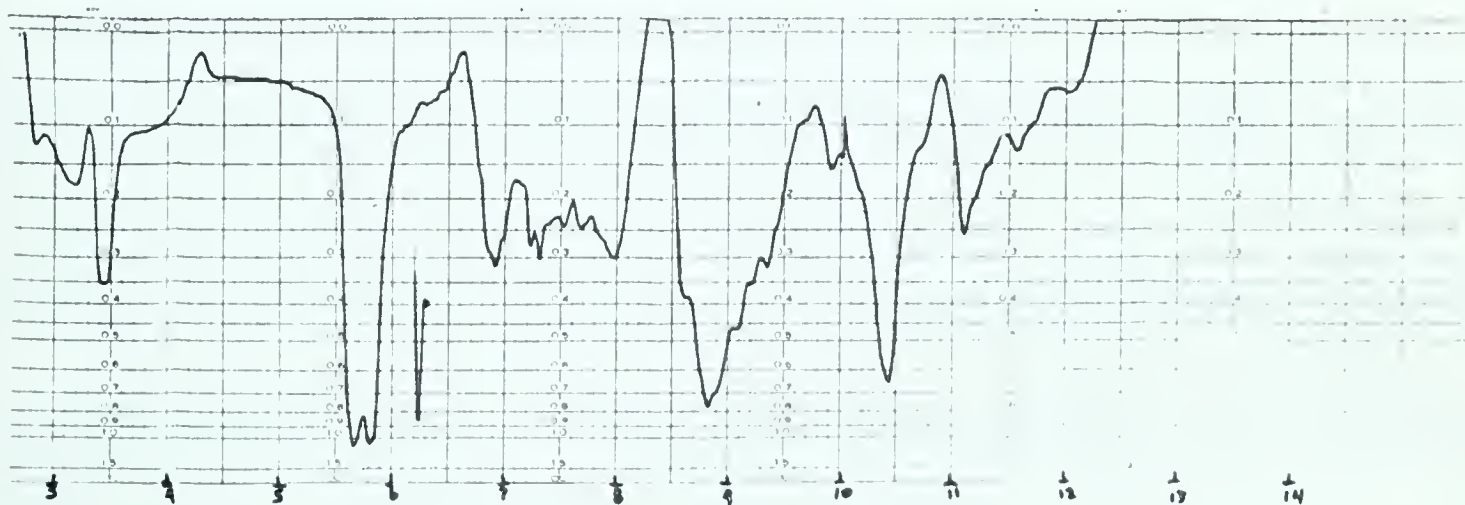


Figure 63. Infrared spectrum of the lactone monoacid 43b.

of a shoulder or a peak in the 1745 cm^{-1} region.

Assignment of an endo configuration to the carboxyl group of the lactone monoacid 43b follows from the observation that esterification with diazomethane provided the lactone dimethyl ester 43c identified by melting point, mixture melting point and infrared spectral comparison with authentic material.

An attempt to confirm this structural assignment by conversion of the lactone diacid 43a to maleopimaric acid (28a) by a saponification-dehydration sequence however did not give entirely satisfactory results. Thus, although maleopimaric acid was obtained in greater than 35% yield (isolated as the methyl ester 28b after esterification and chromatography on silica gel) by refluxing the lactone diacid 43a in a 1.1 molar solution of sodium hydroxide for 4 days, there was also obtained an equal amount of the hydroxy diacid 44a, $\text{C}_{24}\text{H}_{36}\text{O}_7$, m.p. $250-52^\circ\text{C}$, which could be isolated from the crude product prior to esterification and chromatography because of its relative insolubility in benzene, in which the C-21 and C-22 carboxyl groups were found to bear a trans relationship to each other. The evidence for this assignment is as follows.

First, the hydroxy acid 44a ($\nu_{\text{max}}^{\text{nujol}}$ 3419, 3350-2400, 1732, 1697 and 1667 cm^{-1}) could not be converted to the anhydride by heating at 170°C for 4 hours. In view of the previously discussed ease with which the cis 1,2 diacids are converted to their anhydrides this thermal stability is considered to provide a good indication of a trans arrangement in the hydroxy triacid 44a. Further evidence was obtained by converting the

hydroxy triacid to the corresponding trimethyl ester 44b, $C_{27}H_{42}O_7$, m.p. 176-78°C, with diazomethane. The ester functions were identified by carbonyl absorption at $\nu=1728\text{ cm}^{-1}$ and 1710 cm^{-1} and by n.m.r. signals at 6.33τ (6H) and 6.27τ (3H). A trans arrangement of the C-21 and C-22 carbomethoxy groups, which can be inferred from the absence of any apparent shielding effects as well as by the lack of infrared absorption at ca. 1745 cm^{-1} , was confirmed by dehydration of the hydroxy triester 44b with phosphorus oxychloride in pyridine to an oily three component product (by t.l.c. analysis) from which dimethyl fumarate could be obtained in 33% yield by heating for 20 hours at 250°C.

Since dehydration of the hydroxy trimethyl ester 44b would be expected to proceed via a trans E-2 elimination process, the anticipated product is the isopropylidene trimethyl ester 45 rather than the endocyclic isomer 32b because of the relative inaccessibility of a trans C-8 hydrogen. This expectation was borne out by the n.m.r. spectrum of the oily dehydration mixture which showed signals at 9.38τ (C-17 methyl of the trans trimethyl ester 32) and 9.18τ (C-17 methyl of the isopropylidene triester 45) in the ratio of 1:4. This latter assignment is consistent with the anticipated decrease in shielding resulting from shifting the double bond to an exocyclic position since this causes not only a decrease in the angle between the methyl group at C-12 and the olefinic bond (see page 14) but also increases the distance between these two centers.

The most plausible explanation for the formation of both maleopimaric acid and the hydroxy triacid 44a involves lactone ring opening



Figure 7. Nuclear magnetic resonance spectrum of the hydroxy trimethyl ester 44b.

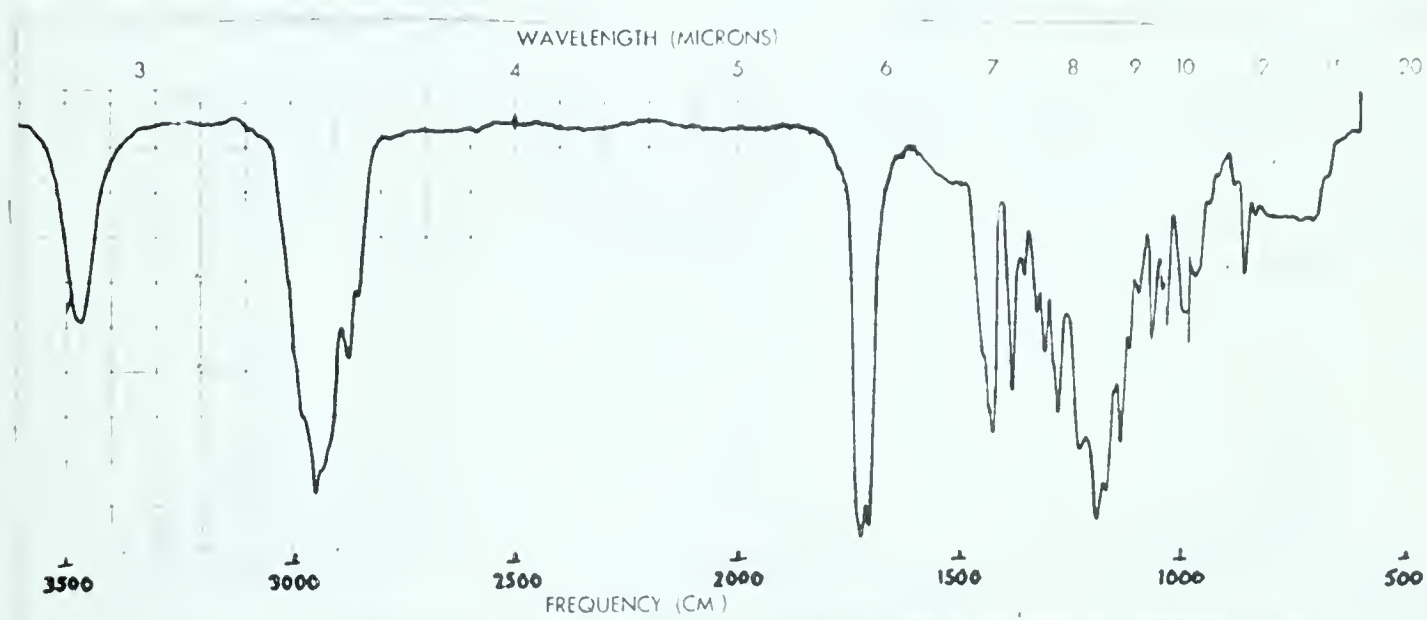
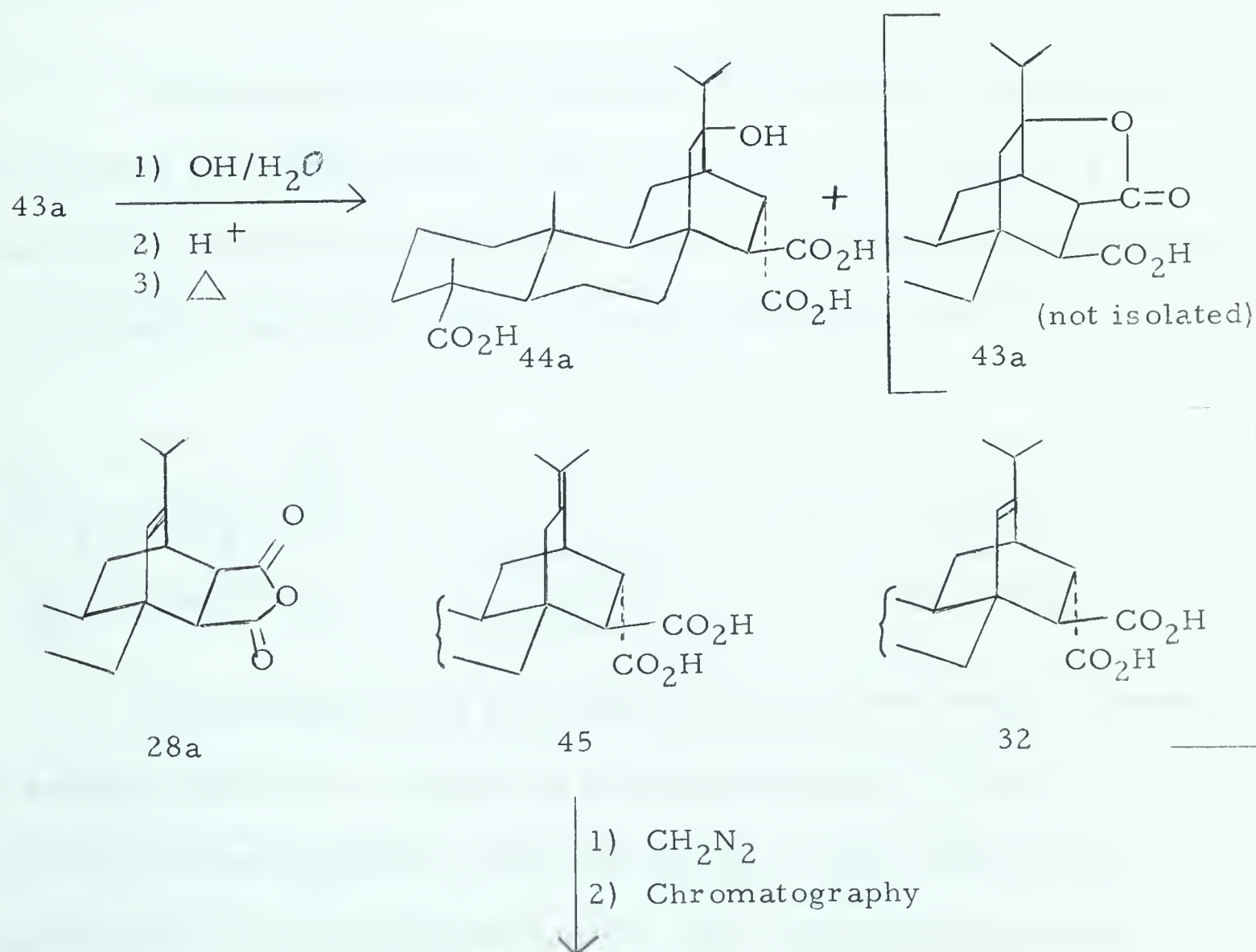
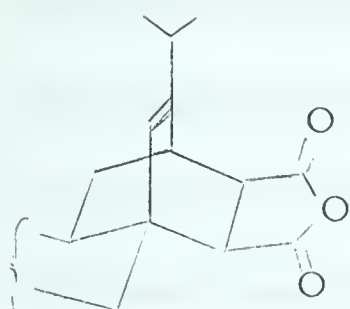


Figure 8. Infrared spectrum of the hydroxy trimethyl ester 44b.

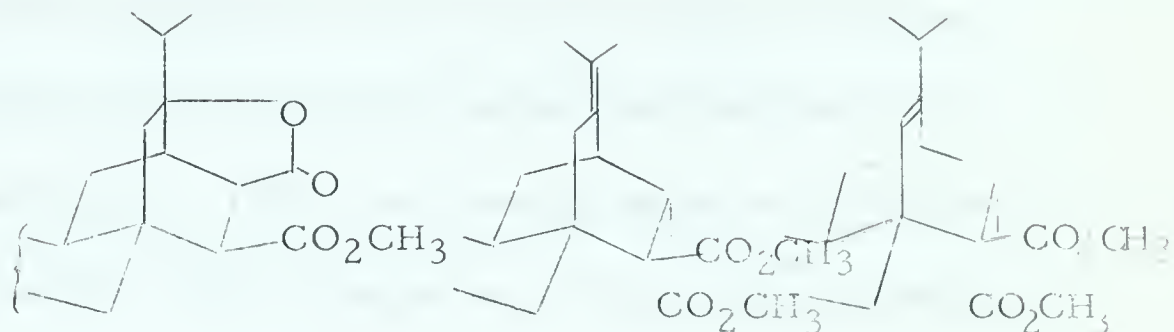
followed by a partial epimerization at C-21. This epimerization, although it has a strong driving force in the 1,3 diaxial interaction between the C-7 hydroxyl and an endo C-21 carboxyl group, is unusual in that it would appear to involve the unfavorable dienolate intermediate $\text{C}=\text{C}(\text{O}^-)_2$. However, the fact that the third carboxyl group of maleopimaric acid could not be titrated in the pK_{MCS} measurements (see page 22) leaves open the possibility that epimerization of a free carboxyl group may be occurring. The assignment of an *exo* C-21 carboxyl group to the hydroxy acid 44a is also supported by its failure to lactonize on treatment with N,N'-dicyclohexylcarbodiimide.



1) CH_2N_2
2) Chromatography
↓



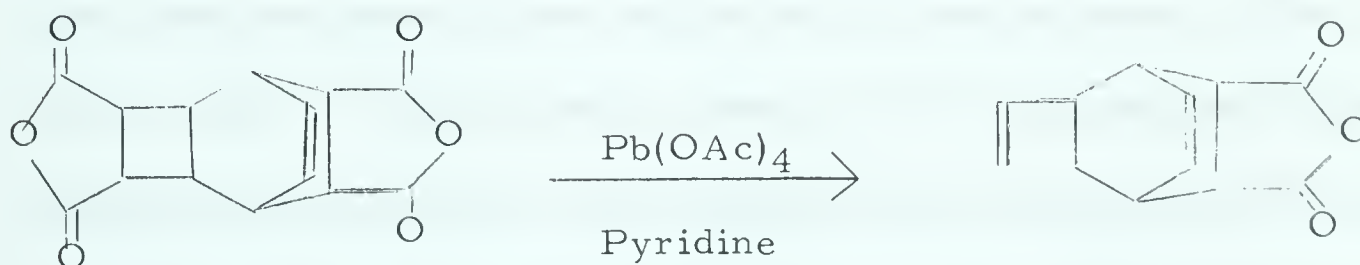
28b



43c

d) Oxidative Bisdecarboxylations with Lead Tetraacetate in Pyridine Solution.

As the saponification experiments described in the previous section were nearing completion, there appeared in the literature a report of an oxidative bisdecarboxylation of a dimaleic anhydride adduct of benzene to a cyclobutene derivative with lead tetraacetate in pyridine⁶⁰.



Encouraged by the possibility that this solvent might alleviate the solubility problems encountered in the unsuccessful attempt to decarboxylate fumaropimaric acid (32a) and at the same time permit decarboxylation of the anhydride function itself, the lead tetraacetate decarboxylation studies were resumed.

Maleopimaric acid, the first compound to be investigated, was readily decarboxylated with lead tetraacetate in pyridine at 50°C. However chromatographic purification of the crude product on silica gel showed that the reactive site was not the anhydride function, but rather the C-15 carboxyl group. This was readily apparent from the infrared spectrum of the oily olefin mixture 46, $C_{23}H_{30}O_3$, obtained in 32% yield on elution with benzene. The infrared spectrum of this oil exhibited the characteristic anhydride absorption bands at 1855 cm^{-1} and 1775 cm^{-1} but no carboxyl absorption in the 1700 cm^{-1} region. The olefinic nature was evident by the presence of weak absorption at $\nu=3080$, 3030 and 1636 cm^{-1} , and from a strongly positive tetranitromethane test.

The presence of three double bond isomers was inferred from the fact that the n.m.r. spectrum contained C-CH₃ signals at 9.55, 9.48, and 9.27 τ (intensity ratio $\simeq 2:2:1$). Two equal intensity signals at 5.52 and 5.28 τ are in the range expected for exo methylene protons and therefore provide good indication for the formation of the $\Delta^{1,16}$ isomer 46a. A third olefinic peak at 4.77 τ , approximately one-half as intense as the first two, was assigned to the hydrogen at C-2 in the $\Delta^{1,2}$ olefin 46b. The formation of this isomer, as well as the tetrasubstituted $\Delta^{1,11}$ isomer 46c, was further substantiated by a strong peak at 8.38 τ representing the vinylic C-16 methyl group. The olefinic proton at C-8 was represented in all three isomers by a single peak at 4.40 τ .

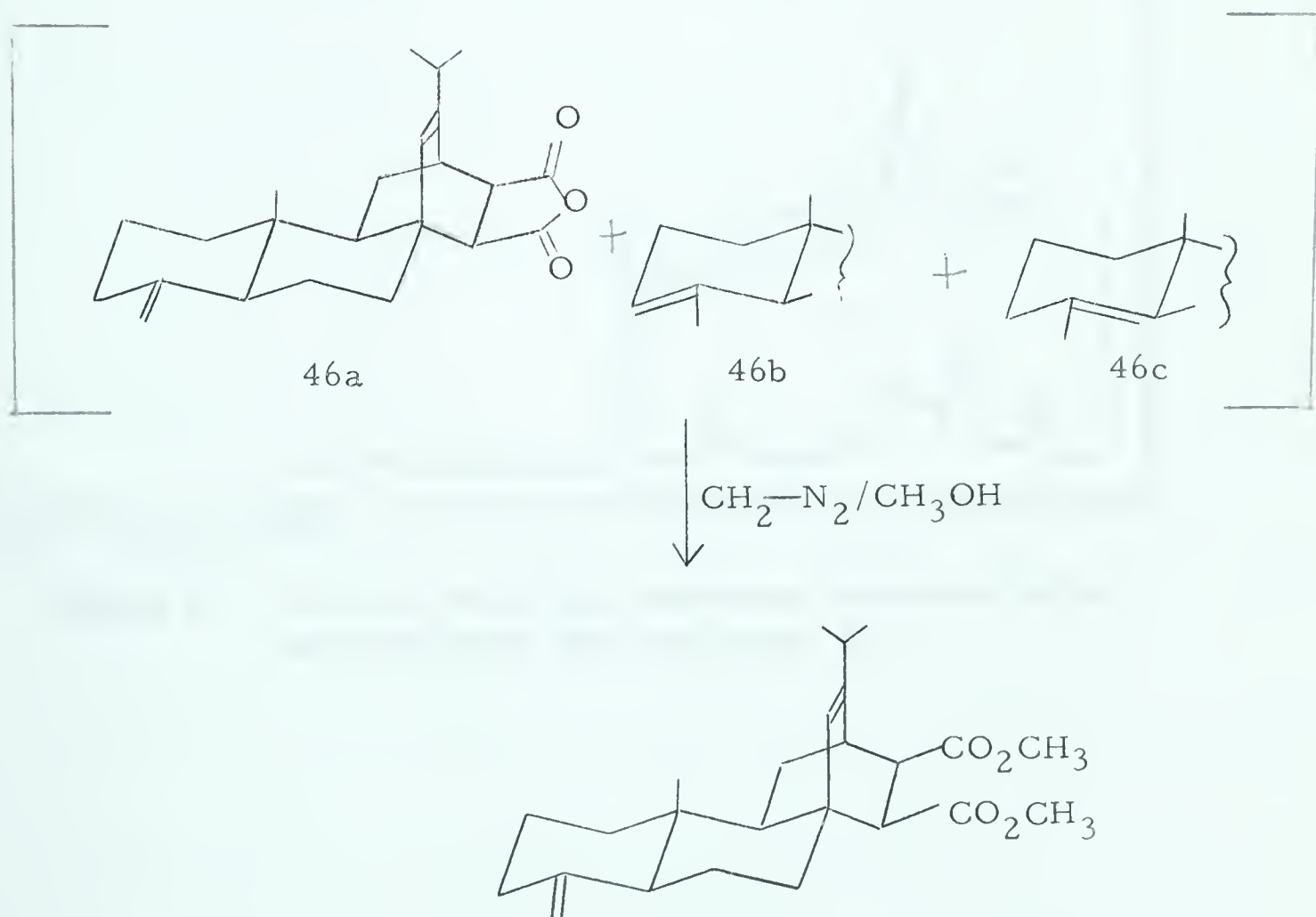
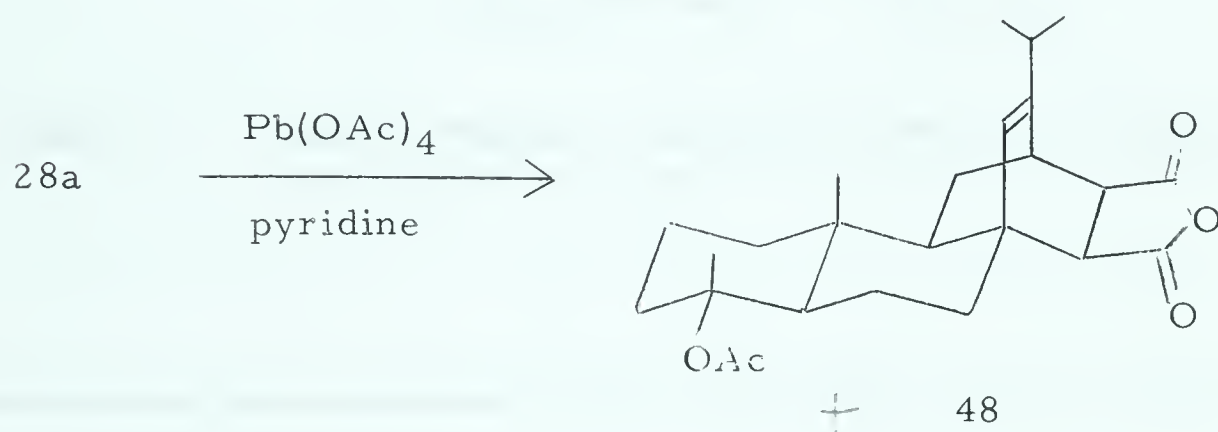
Esterification of the oilyolefinic mixture with diazomethane in methanol solution, followed by chromatography on alumina, enabled the

isolation of the exo methylene dimethyl ester 47, $C_{25}H_{36}O_4$, m.p. 121-23°C. The exo methylene group was characterized by two 1 proton signals at 5.53 and 5.28 τ and the endo C-21 and C-22 carbomethoxyl groups by a six proton signal at 6.45 τ as well as by a strong band in the infrared spectrum at 1750 cm^{-1} . The angular methyl at C-12 which appeared as a three proton signal at 9.55 τ may be shielded by the exo methylene group since this value is somewhat higher than normally encountered in $\Delta^{7,8}$ olefins.

Continued elution of the initial reaction product yielded a second fraction from which there was obtained the crystalline acetoxy anhydride 48, $C_{25}H_{34}O_5$, m.p. 181-83°C after recrystallization from benzene-Skellysolve and ethyl acetate. The anhydride function was identified by infrared absorption at 1845 cm^{-1} (m) and 1785 cm^{-1} (s), while the acetoxy group was characterized by a band in the infrared at 1725 cm^{-1} and a three proton signal at 8.04 τ in the n.m.r. spectrum. Location of the acetoxy function at C-1 was easily established from the deshielded nature of the C-16 methyl group ($\tau=8.60$). The final structural detail, that of assigning an equatorial configuration to this group, was arrived at by the following considerations.

An axially orientated acetoxy group would be expected to deshield the angular methyl at C-12 by ca. 0.1 p.p.m.⁶¹ because of their 1,3 diaxial arrangement. The fact that this methyl group in the acetoxy anhydride 48 resonates at virtually the same position as in methyl maleo-pimarate (28b) (9.43 and 9.41 τ respectively) therefore argues against

such an arrangement and leads to the conclusion that the acetoxy group in the anhydride 48 occupies an equatorial position. This assignment is consistent with the conclusion reached on the basis of other recently reported examples of lead tetraacetate decarboxylations^{63,62} that incorporation of an acetoxyl group occurs predominately, if not exclusively, from the least hindered side of the molecule.



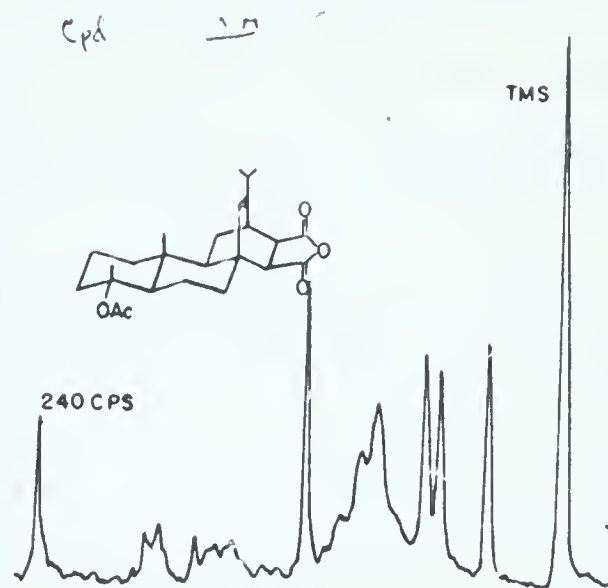


Figure 9. Nuclear magnetic resonance spectrum of the acetoxy anhydride 48. at 60 mc.

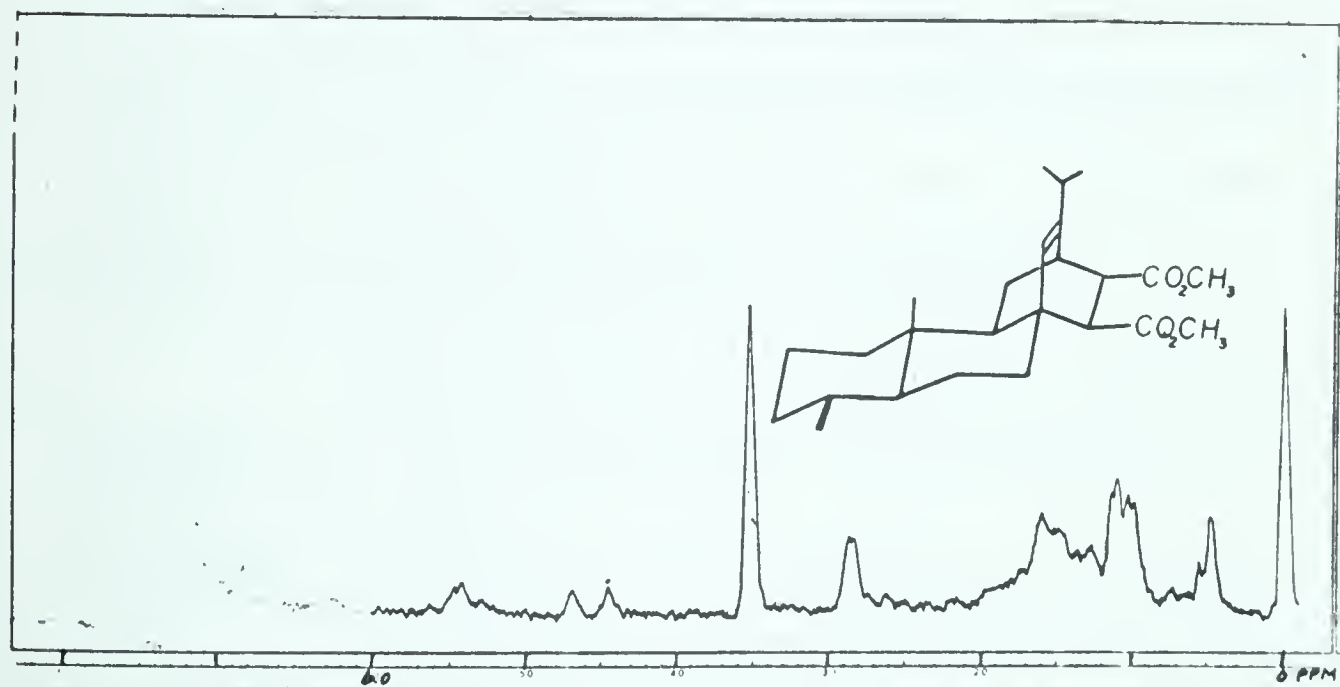


Figure 10. Nuclear magnetic resonance spectrum of the exomethylene dimethyl ester 47.

In order to obtain additional support for the assignment of a C-1 acetoxyl group in the anhydride 48, an analogy was sought in the decarboxylation of phenylacetic acid with lead tetraacetate in pyridine. Column chromatography of the reaction product on alumina provided an early running crystalline hydrocarbon fraction (4% yield) followed by an oily ester fraction. G.L.C. analysis with Ucon oil (R) and silicone grease (O) columns showed that this second fraction was composed of two major and two minor components. From a comparison of the retention times of one of the major components (815 sec., R column and 195 sec., O column) with that of benzyl acetate (821 sec., and 194 sec.) it was concluded that benzyl acetate is in fact a product of the decarboxylation and hence that decarboxylation under the conditions employed with maleopimaric acid can lead to incorporation of an acetoxyl group at the carbon bearing the carboxyl group.

One of the minor components was tentatively identified as methyl phenylacetate from a comparison of its retention time with that of authentic sample (891 and 880 seconds respectively on an Ucon oil column).

Recrystallization of the solid hydrocarbon fraction from 95% ethanol gave clusters of needles, m.p. 52-53°C, identified as bibenzyl by melting point (reported 52-53°C), mixture melting point and infrared spectral comparison with authentic material. The isolation of this dimer suggest the possibility that decarboxylation has, at least in part, occurred via a free radical mechanism.

With the need for protecting the C-15 carboxyl group now

clearly established, attention was next given to the reaction of methyl maleopimarate (28b) and methyl fumaropimarate (42) with lead tetraacetate in pyridine.

In two experiments with methyl maleopimarate, one conducted at 50°, the second at 97°, the only reaction observed was a decomposition of lead tetraacetate in the pyridine solvent, characterized in the former case by a slow change in the solution colour and in the second, by a vigorous and almost instantaneous evolution of gas. In both experiments methyl maleopimarate was recovered in greater than 80% yield. The instability of lead tetraacetate in hot pyridine was confirmed by the fact that the evolution of gas, the colour and temperature changes observed in these two experiments could also be duplicated in control experiments involving lead tetraacetate and pyridine alone.

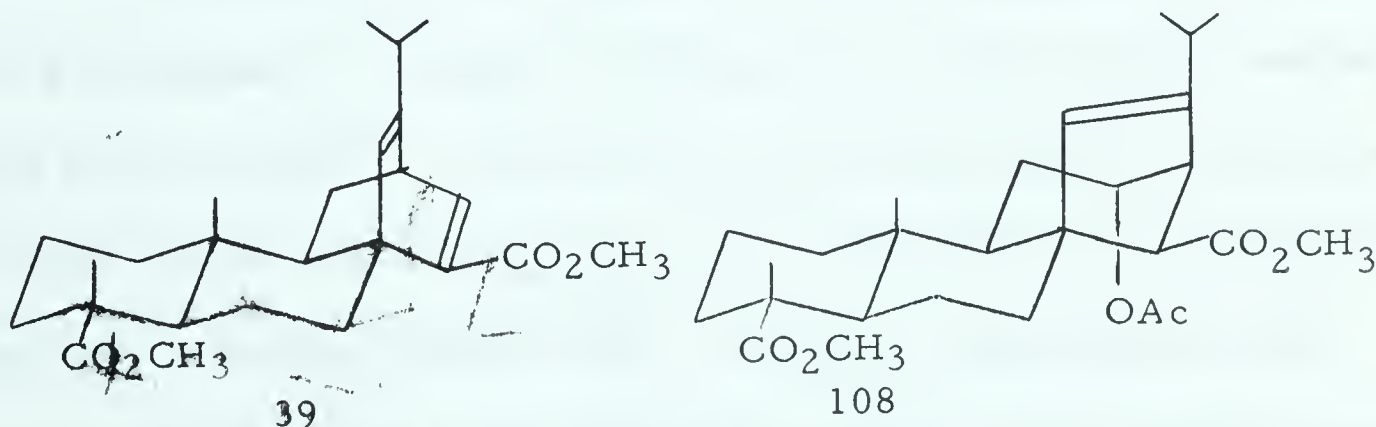
The reaction of lead tetraacetate with methyl fumaropimarate (42) in several solvent systems including pyridine has been given a considerable amount of attention and is discussed in a later section of this thesis (see Section 3). For this reason the results will now be described very briefly and only insofar as they influenced the direction of further research relating to the correlation with atisine.

Of the several products isolated from the reaction in pyridine solution, one, obtained as an oil in ca. 10% yield, was shown (Section 3, pg. 202) to be the desired diene 40 resulting from an oxidative bisdecarboxylation of the C-21 and C-22 carboxyl groups. However the reaction was complicated by the occurrence of a considerable amount of lactonization between

the C-22 carboxyl and C-8 which at that time was felt to be primarily responsible for the unsatisfactory yield of diene. It was therefore concluded that in order to improve the yield of decarboxylation product, the lactonization process would have to be blocked by a suitable alteration of either the C-22 carboxyl or the $\Delta^{7,8}$ olefinic group.

Two compounds which meet this requirement are the mono acid 41 and the lactone mono acid 43b. However preliminary attempts to adapt the lead tetraacetate-pyridine reaction to these compounds in the hope of isolating the synthetically useful acetoxy derivatives met with unpromising results and the studies were discontinued.

In the case of the mono acid 41 decarboxylation gave, after chromatography on alumina, a 7% yield of colorless oil which, from its spectral properties, appeared to be a mixture of the rearranged acetate 108 and the unrearranged $\alpha\beta$ -unsaturated ester 39 in a 14:1 ratio. These results are discussed in greater detail in Section 3 of this thesis along with more recent decarboxylation experiments on the mono acid 41 in acetic acid solution.



Similarly, decarboxylation of the lactone mono acid 43b with lead tetraacetate in pyridine yielded only intractable oils ($\nu=3620, 3480$

(OH), 1740 cm^{-1} ($>\text{C}=\text{O}$)) after chromatography on neutral alumina.

As a consequence of these two unsuccessful attempts to extend the lead tetraacetate/pyridine decarboxylation to mono acids, it was decided to adapt the bisdecarboxylation to a compound not containing the complicating $\Delta^{7,8}$ olefinic bond in the hope that this would improve on the modest yield encountered in the formation of diene 40. However, because of the obvious value of the double bond in removing the isopropyl group, this decision required the development of a method for first degrading the three carbon side chain of maleopimaric acid, following which the task of applying the bisdecarboxylation reaction to a suitable non-olefinic derivative could be resumed. The next section describes the results of two approaches to this problem.

III. DEGRADATION OF THE ISOPROPYL SIDE CHAIN IN MALEO-PIMARIC ACID.

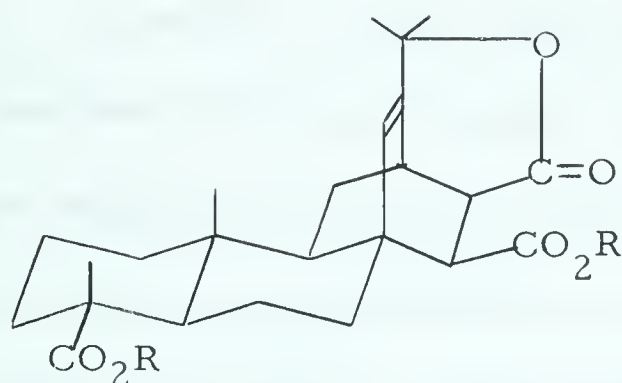
(a) Attempted Ozonolysis of the Unsaturated Lactone Dimethyl Ester 50b.

This approach was suggested by a reinvestigation of the potassium permanganate oxidation of maleopimaric acid originally studied by Ruzicka and La Lande³⁷. These workers had succeeded in isolating an unsaturated lactone diacid, $\text{C}_{24}\text{H}_{32}\text{O}_6$, m.p. $211-12^\circ\text{C}$, to which they had assigned the δ lactone structure 49a. However, examination of the infrared spectrum of this compound and the corresponding dimethyl ester, $\text{C}_{26}\text{H}_{36}\text{O}_6$, m.p. $183.5-5.5^\circ\text{C}$, (reported $182-84^\circ\text{C}$) in these laboratories

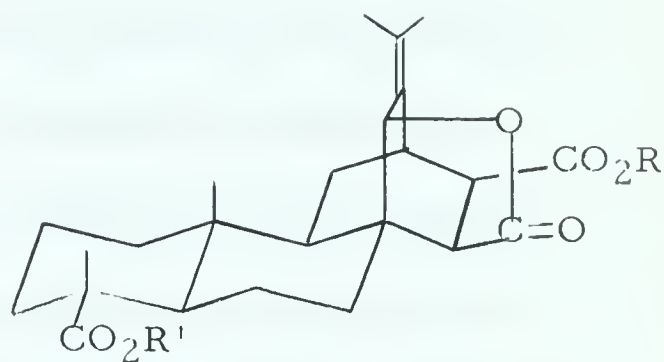
showed the presence of strong absorption at 1772 cm^{-1} and 1771 cm^{-1} respectively, thereby suggesting that it probably contained a γ lactone and not the δ lactone function as originally postulated. This suspicion was strengthened by a comparison with the infrared spectrum of the saturated lactone diacid 43a and dimethyl ester 43c (ν_{max} 1774 cm^{-1} and 1772 cm^{-1} respectively), and it was originally thought that the two might differ only in that the former contained an isopropenyl group instead of the isopropyl group present in the saturated lactone 43.

An attempt to correlate the two lactones through catalytic hydrogenation of the unsaturated lactone dimethyl ester, however, was unsuccessful. Under mild conditions (room temperature / atmospheric pressure) only the starting material was recovered. More vigorous conditions (120°C / 700 p.s.i. for 26 hours) resulted in hydrogenolysis of the lactone ring and subsequent conversion to methyl maleopimarate (28b), identified by melting point ($216-18^{\circ}\text{C}$) and infrared spectral comparison with authentic material. This resistance towards hydrogenation is interpreted as supporting either the original structure 49 or the isopropylidene lactone 50 but seemed to rule out an isopropenyl structure because of the lack of any obvious steric opposition to hydrogenation. From the infrared data already discussed, it is obvious that the latter alternative provides a more satisfactory rationalization of the experimental data.

Formulation of the unsaturated lactone in terms of the isopropylidene structure 50 was confirmed by the following spectral properties of the dimethyl ester. From the n.m.r. spectrum, it was



- 49 a) $R=H$
b) $R=CH_3$



- 50 a) $R=R'=H$
b) $R=R'=CH_3$
c) $R=H; R'=CH_3$

possible to establish the presence of an isopropylidene group both by a six proton signal at 8.20τ , assigned to the vinylic C-19 and C-20 methyls, and by the extent of shielding shown by the angular methyl at C-12 which is similar to that encountered in the isopropylidene trimethyl ester 45 (9.26τ and 9.18τ respectively). A one proton signal at 4.98τ , well outside the range encountered for a C-8 vinylic hydrogen ($4.40-4.63\tau$), is readily assigned to the C-8 proton deshielded by an acyloxy group. The C-21 β carbomethoxyl group, eclipsing the lactonic carbonyl, was identified by the characteristic high frequency infrared band at 1745 cm^{-1} , while the ester group at C-1 was represented in this case by absorption at 1728 cm^{-1} †.

Taking into consideration the hindered nature of the $\Delta^{7,8}$ olefinic bond in maleopimaric acid, already demonstrated by its resistance towards hydrogenation, formation of the unsaturated lactone diacid 50a can be best visualized as involving an allylic oxidation at C-18 followed

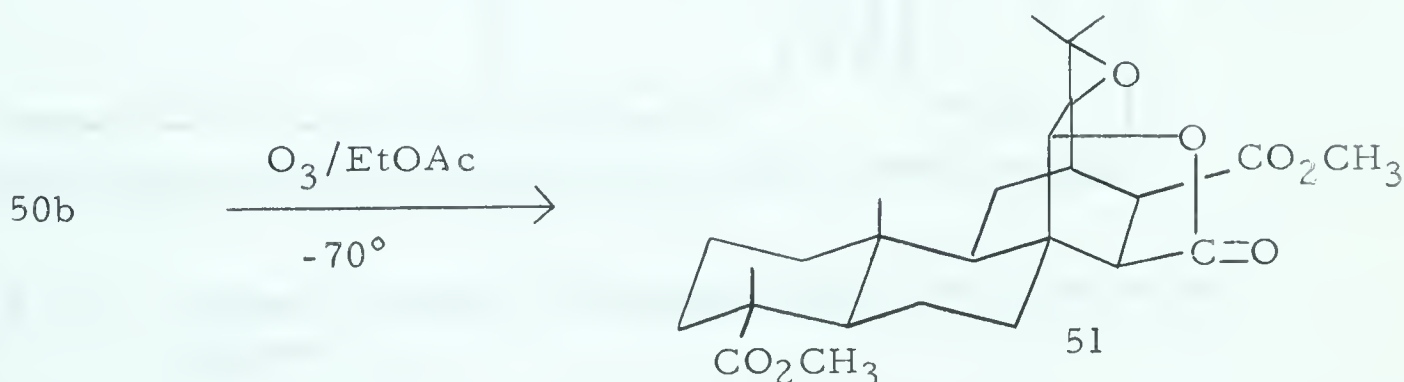
† Following the completion of this phase of our investigations the revised structure 50a for the unsaturated lactone diacid was independently proposed by L. H. Zalkow et al⁶⁴.

by an allylic rearrangement with simultaneous lactonization at C-8.

In order to obtain chemical confirmation for the isopropylidene structure 50 and at the same time investigate the possibility of using the unsaturated lactone to remove the isopropyl group of maleo-pimaric acid, an attempt was made to cleave the double bond in the unsaturated lactone diester 50b with ozone. The reaction, which was conducted in ethyl acetate at -70°C , however was found to take a different course yielding instead the dimorphic oxido lactone 51, $\text{C}_{26}\text{H}_{36}\text{O}_7$, m.p. $145-47^{\circ}\text{C}$; $156-58^{\circ}\text{C}$.

Spectroscopic evidence for the incorporation of an oxygen atom across the isopropylidene double bond was found in the disappearance of a weak band at 1684 cm^{-1} present in the infrared spectrum of the starting material and from an upfield shift of the isopropylidene methyls from 8.20τ to 8.61 and 8.57τ in the oxido lactone 51.

The C-21 and C-15 carbomethoxy groups were identified, as before by infrared absorption at 1740 cm^{-1} and 1724 cm^{-1} respectively as



well as by 3 proton n.m. r. signals at 6.34 and 6.32τ .

Formation of epoxides with ozone has been observed previously with sterically hindered double bonds and is considered to involve electrophilic attack by ozone followed by loss of oxygen and formation of the epoxide

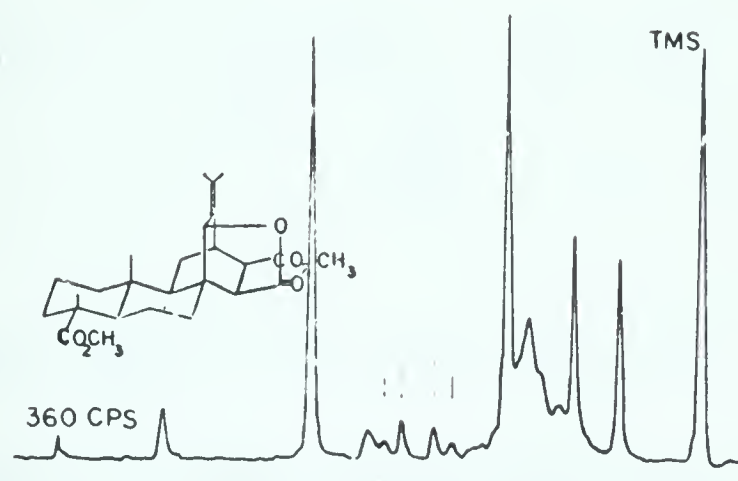


Figure 11. Nuclear magnetic resonance spectrum of the unsaturated lactone dimethyl ester 50b. at 60 mc.

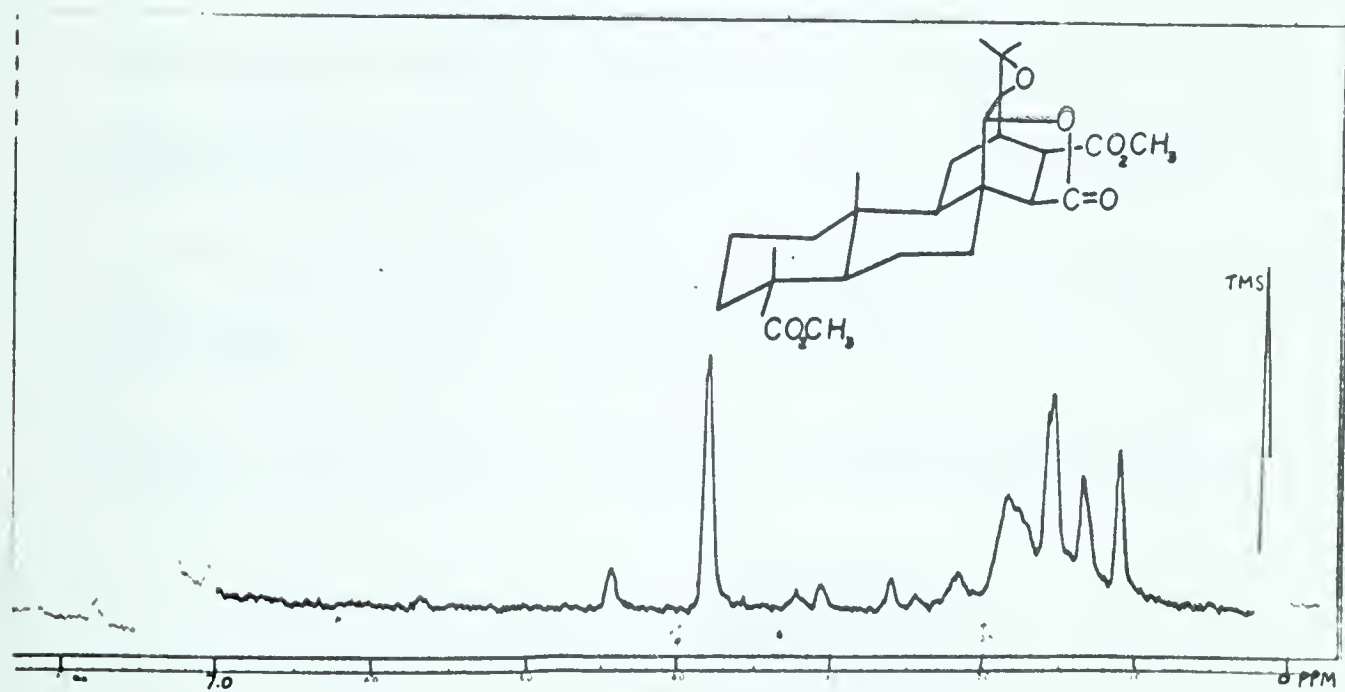
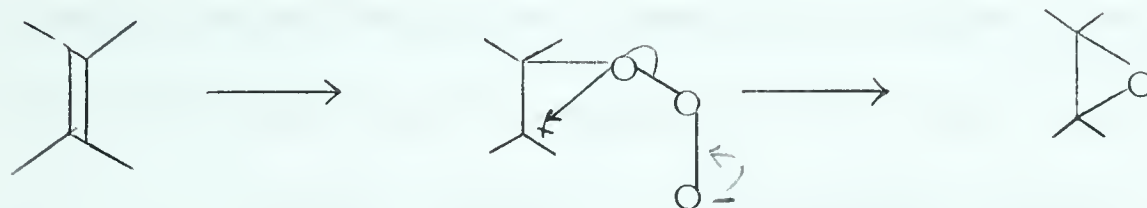


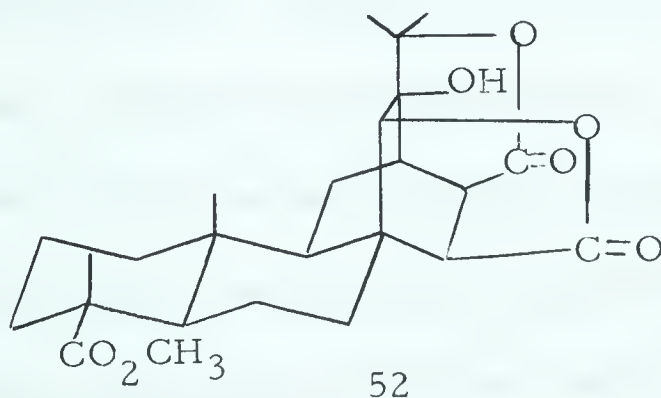
Figure 12. Nuclear magnetic resonance spectrum of the oxido lactone 51.

as shown below⁶⁵



This conversion of the unsaturated lactone dimethyl ester 50b to the oxido lactone therefore provides direct chemical evidence for a hindered, tetrasubstituted isopropylidene group assumed earlier to explain the resistance of the unsaturated lactone diester towards hydrogenation.

An attempt to open the oxide ring to the α glycol, in the hope that this might be cleaved with either periodic acid or lead tetraacetate, was also unsuccessful. The α glycol expected from hydrolysis of the oxido lactone 51 with perchloric acid in aqueous dioxane was apparently unstable, undergoing a second lactonization to yield the hydroxy dilactone 52, $C_{25}H_{34}O_7$, m.p. 345-49°C (dec.).



The γ and δ lactones were identified by infrared absorption bands at 1773 cm^{-1} and 1747 cm^{-1} . The carbomethoxyl group at C-1 was characterized by infrared absorption at 1720 cm^{-1} and by a three

proton signal at 6.54τ in the n.m.r. spectrum ($\text{CF}_3\text{CO}_2\text{H}$ solvent). Finally, the hydroxyl group appeared as a broad absorption band at 3435 cm^{-1} and one proton signal at 7.52τ in the n.m.r. spectrum.

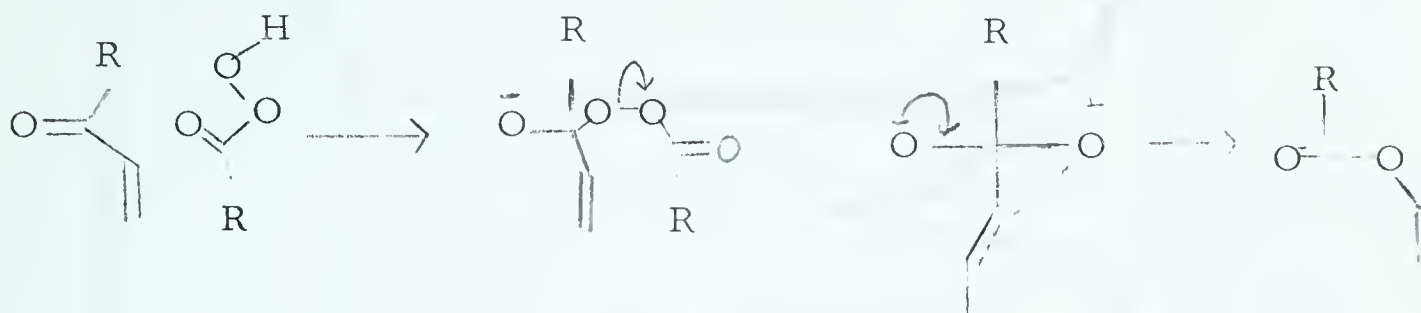
Further support for the assigned structure was found in the resistance of the hydroxy dilactone 52 to attempted dehydration with phosphorus oxychloride in pyridine as well as in its stability towards both periodic acid and diazomethane.

b) Formation and Reactions of the Methyl Ketone 38.

Baeyer-Villiger Oxidation to the Bicyclic Ketone 59.

The second approach to degrading the isopropyl side chain of maleopimaric acid was suggested by the reported oxidation of the cis ester trimethyl³⁴ to the methyl ketone 38 with ozone⁴⁹. A survey of the literature indicated that Baeyer-Villiger oxidation, either on the methyl ketone 38 or the corresponding saturated ketone which would result from a successful lithium-ammonia reduction of the $\Delta^{7,8}$ olefinic bond, should complete the degradation, placing in the one case an enol acetate at C-7, and in the other a saturated acetoxyl group. Thus, several examples were available in which peracids preferentially attacked the carbonyl group of $\alpha\beta$ unsaturated ketones, a competitive epoxidation of the olefinic bond, even when sterically unhindered, being only of minor importance^{66,67}. The sole product of these oxidations was invariably the enol acetate resulting from migration of the vinyl group, a selectivity which parallels similar rearrangements of vinyl groups to electron deficient carbon^{68,69}.

and which may therefore proceed by a homoallylically stabilized intermediate as proposed for this latter system⁶⁸.



The expectation that a Baeyer-Villiger oxidation on the saturated methyl ketone would result in migration of the secondary carbon was based on the established order of migratory aptitudes⁷⁰, exemplified in the diterpene field by the conversion of several methyl ketones to the acetates^{11,23,71}.

The methyl ketone 38 used in these investigations was prepared by ozonizing a solution of the cis trimethyl ester 34 in acetic acid solution until the ultraviolet absorption at 240m μ reached a maximum. Following the method reported earlier⁴⁹, the methyl ketone 38, C₂₆H₃₆O₇, m.p. 168-68.5° (reported 168-69°) was isolated in ca. 40% yield via the Girard T derivative.

The conjugated carbonyl chromophore was identified by ultraviolet absorption at 240 m μ ($\epsilon=11,000$) and 305 m μ ($\epsilon=65$) and by strong infrared absorption at 1667 cm⁻¹. The trisubstituted olefinic bond was characterized by a weak band at 1610 cm⁻¹ and a one proton signal at 3.22 τ in the n.m.r. spectrum. The paramagnetic shift of the olefinic proton at C-8 as well as the bathochromic shift of the carbonyl $n \rightarrow \pi^*$ absorption and the olefinic stretching vibration are all

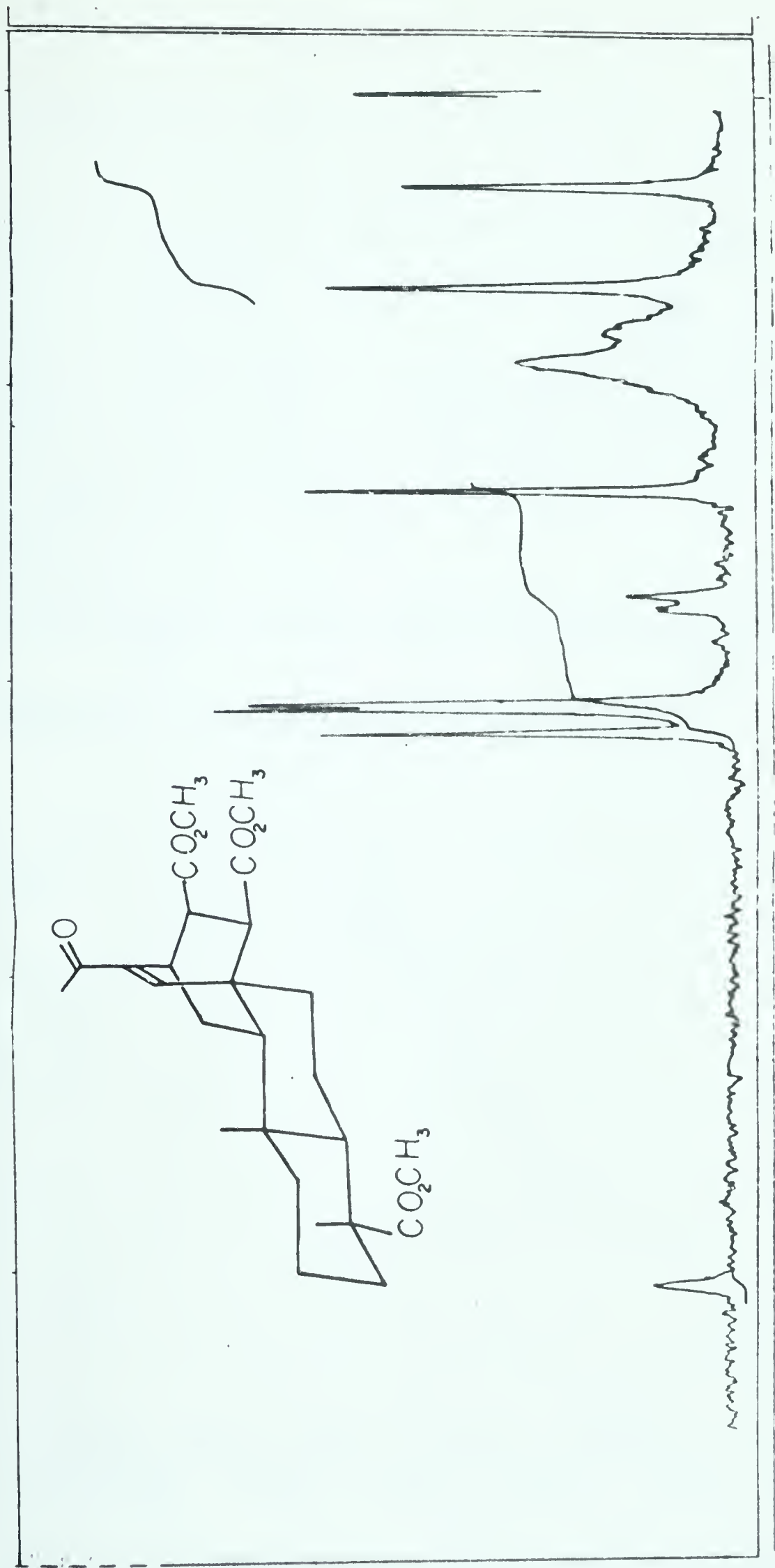


Figure 13. Nuclear magnetic resonance spectrum of the methyl ketone 38.

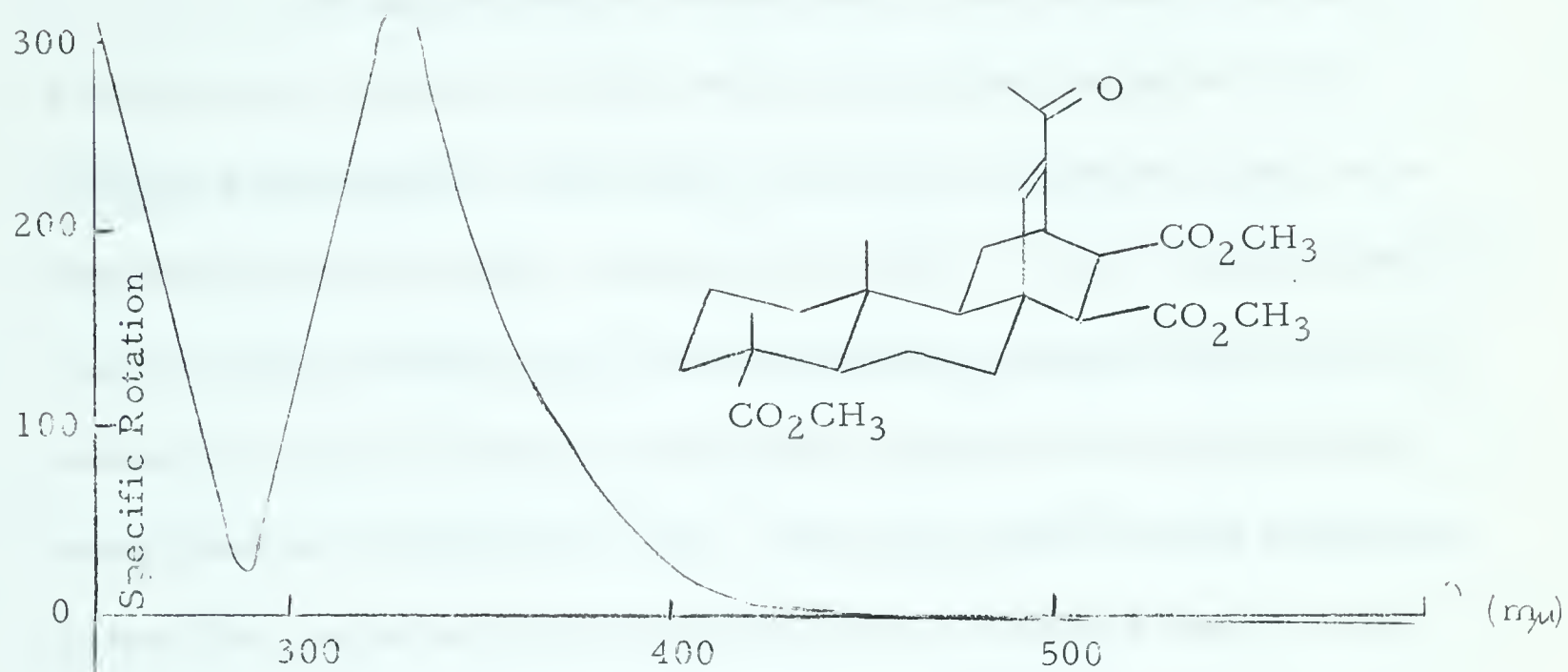


Figure 14. R.D. Curve of the Methyl Ketone 38.

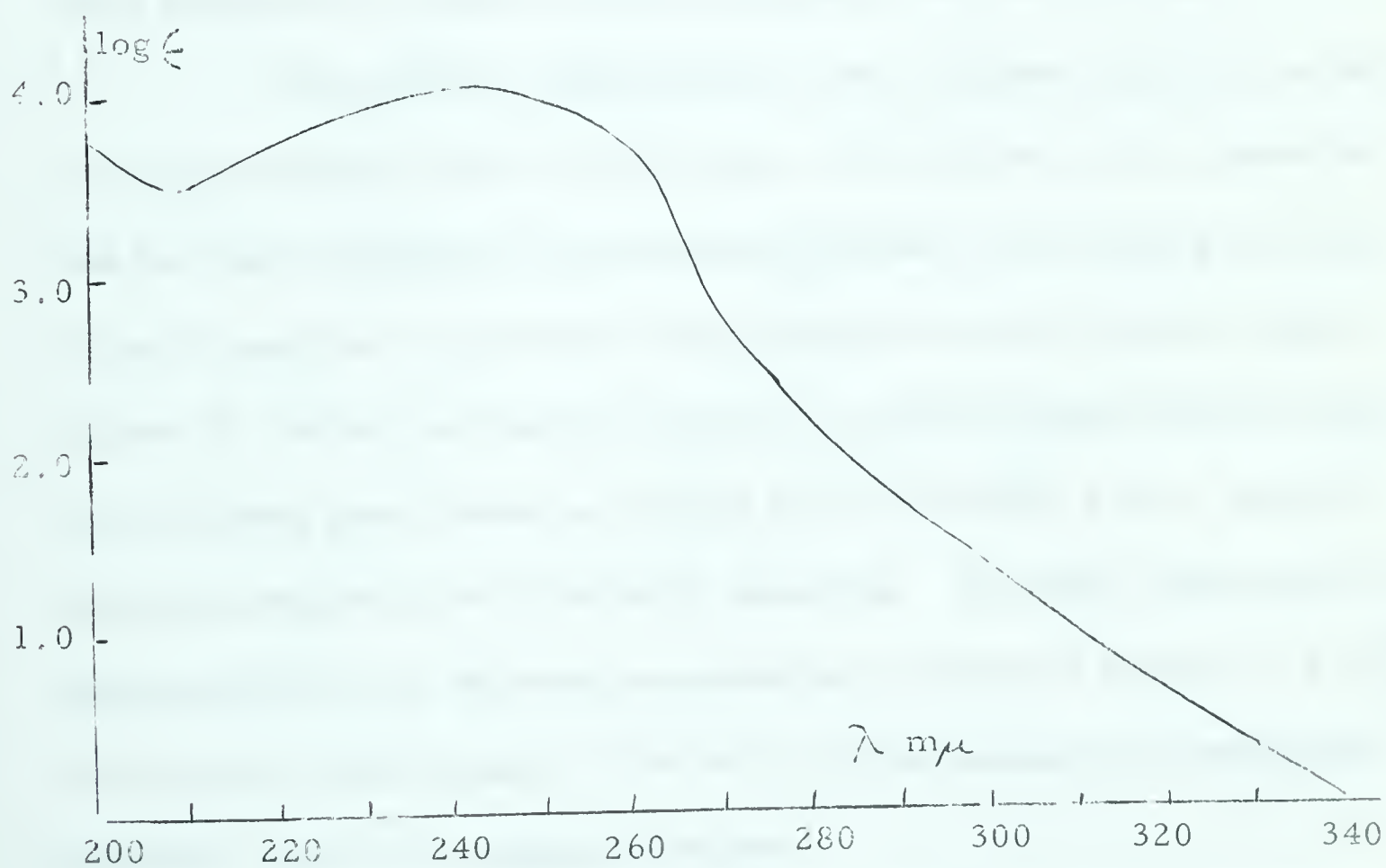


Figure 15. Ultraviolet Spectrum of the Methyl Ketone 38.

consistent with the proposed conjugated system.

The methyl ketone moiety was characterized by a three proton n.m.r. signal at 7.63τ , while the angular methyl at C-12, showing a diamagnetic shift of ca. 0.10 p.p.m. relative to the unconjugated endocyclic olefins, appeared at 9.49τ . This enhanced shielding was also observed for one of the carbomethoxyl groups which was now located at 6.51τ . The remaining ester signals were unexceptional, being found at 6.45τ and 6.34τ . The exact cause for this alteration in the shielding effect is uncertain but may be due to a change in the polarization of the carbon-carbon double bond¹⁰⁴.

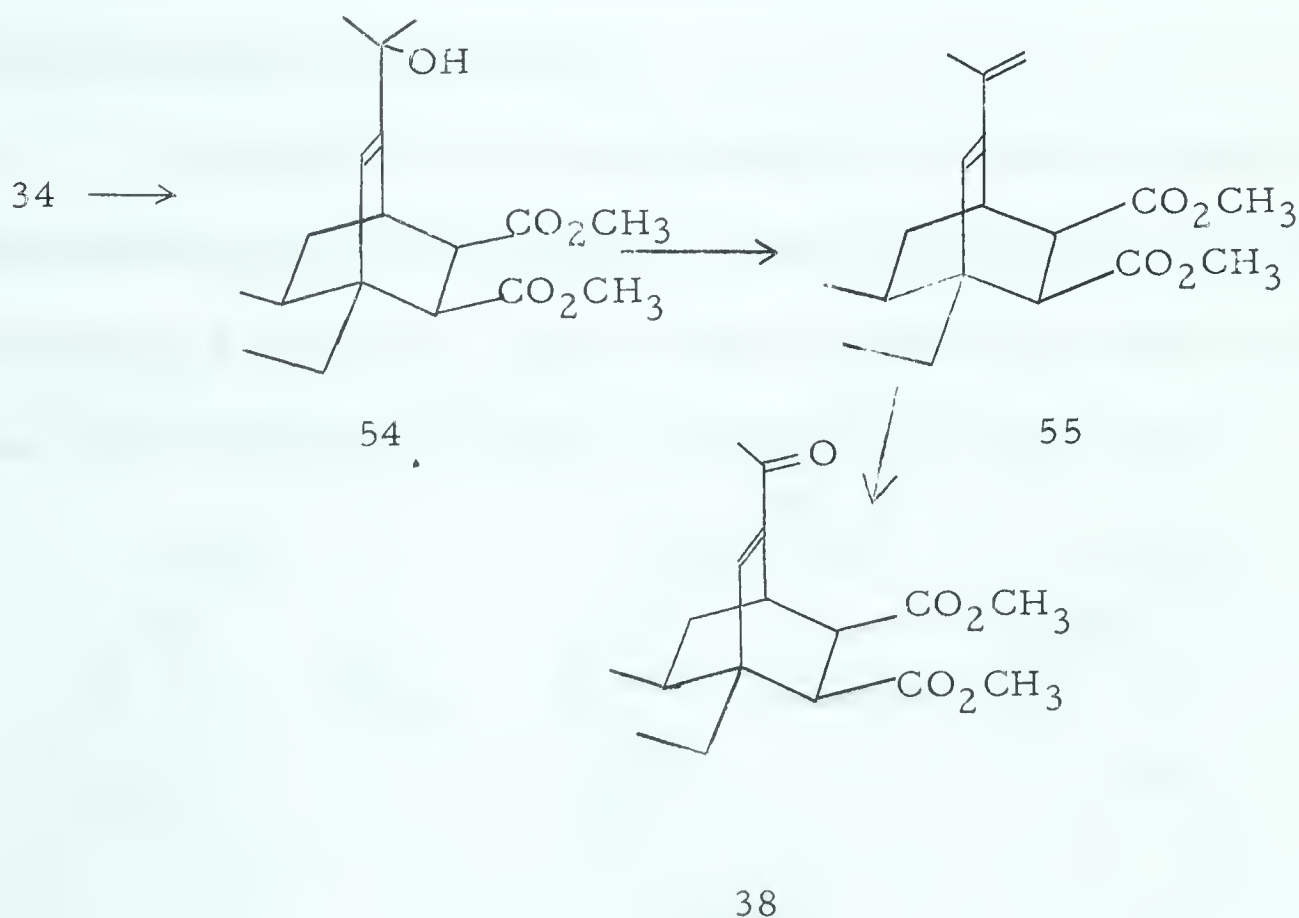
The eclipsed C-21 and C-22 carbomethoxy functions were again indicated by a high frequency carbonyl band at 1750 cm^{-1} .

Three other compounds have been isolated from the oxidation of the cis trimethyl ester 34 with ozone, all of them in trace amounts. One has been identified as the hydroxy dilactone 52 by melting point and infrared spectral comparison with a sample prepared from the oxido lactone 51, while a second was found to be identical with bicyclic ketone 59 by melting point, mixture melting point, infrared, n.m.r. and RD spectral comparison with authentic material. The third compound was characterized by its infrared spectrum as a hydroxy γ lactone 53 ($\nu_{\text{max}}^{\text{CHCl}_3}$ 3614 (sharp), 3445 (broad), 1774 cm^{-1} (s)) but because of insufficient material, was not investigated further.

Following completion of this work an independent investigation of the reaction between ozone and the cis trimethyl ester 34 has been

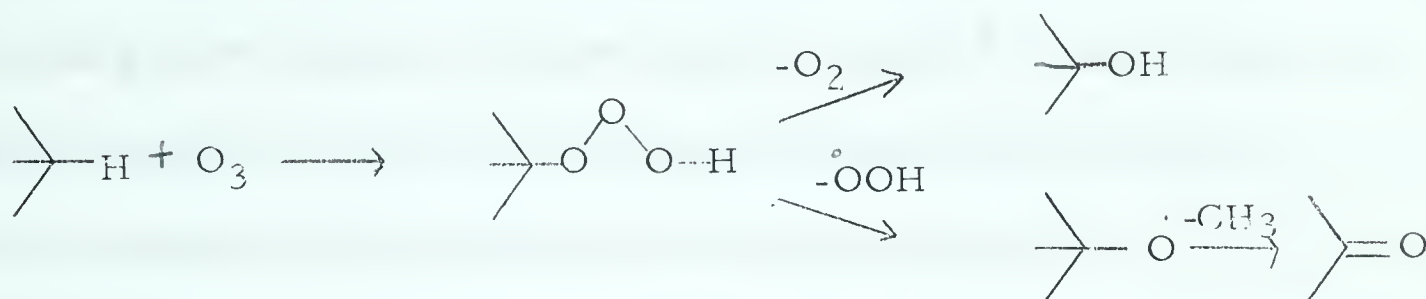
reported⁷². Of the several products isolated, two were shown to be the methyl ketone 38 and the bicyclic ketone 59. A dihydroxy γ lactone was also obtained and characterized but the published spectral data ($\nu_{\text{max}}^{\text{KBr}}$ 3448, 1786 cm^{-1}) did not permit a correlation with the hydroxy lactone 53.

Formation of the methyl ketone 38 has been suggested to involve as intermediates, two compounds which have been isolated from the oxidation, the C-18 hydroxy trimethyl ester 54⁷² and the conjugated diene 55⁴⁹. Selective ozonolysis of the terminal double bond would then provide the methyl ketone 38.



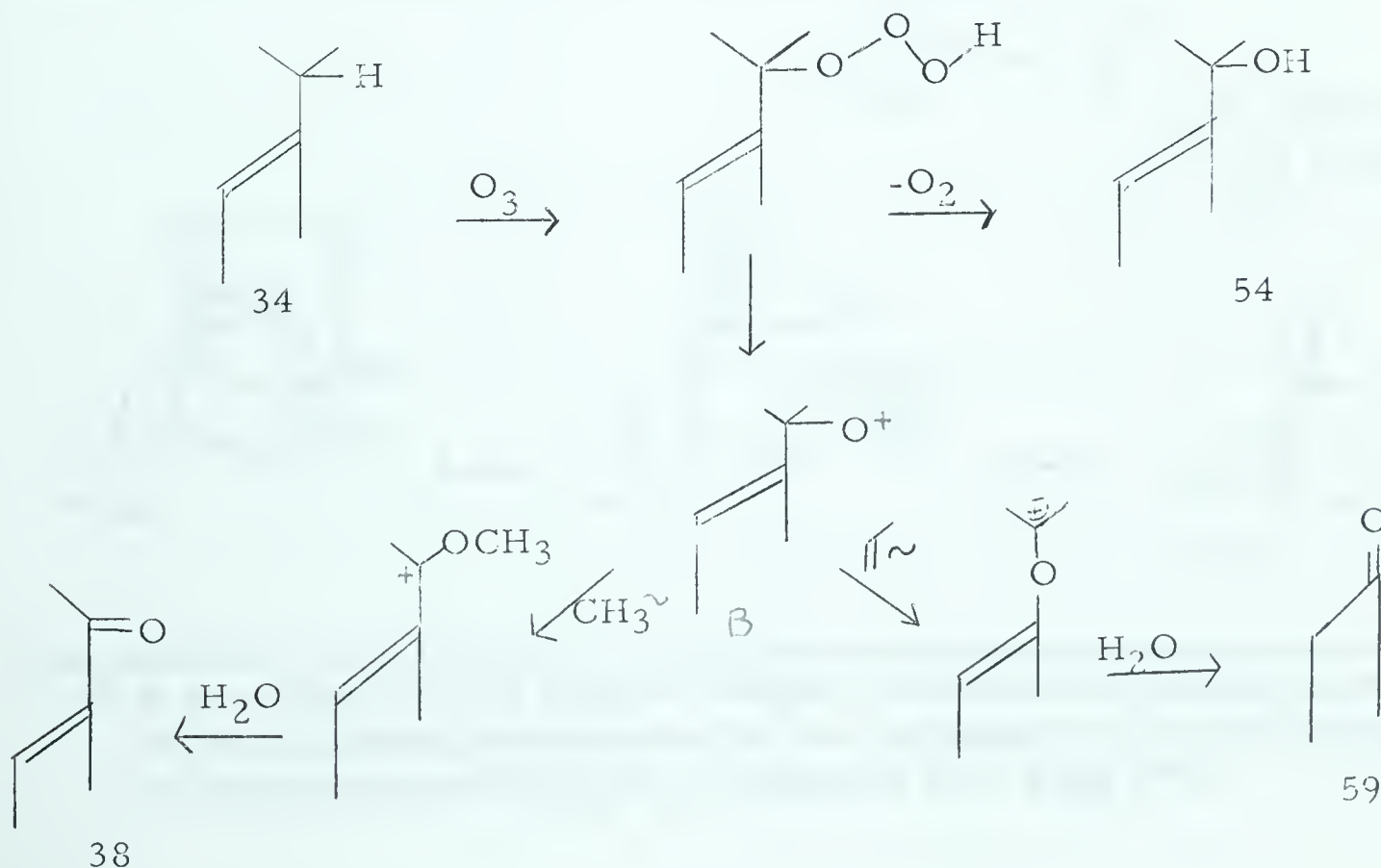
Although this route may contribute to formation of the methyl ketone 38, a second alternative is suggested by the gas phase oxidation of isobutane with ozone which results in an almost complete conversion to a 3:1 mixture of t-butyl alcohol and acetone⁷³. Since the acetone was

shown not to form from t-butyl alcohol, it assumed to form directly from a carbon-carbon cleavage of the alkoxy radical.



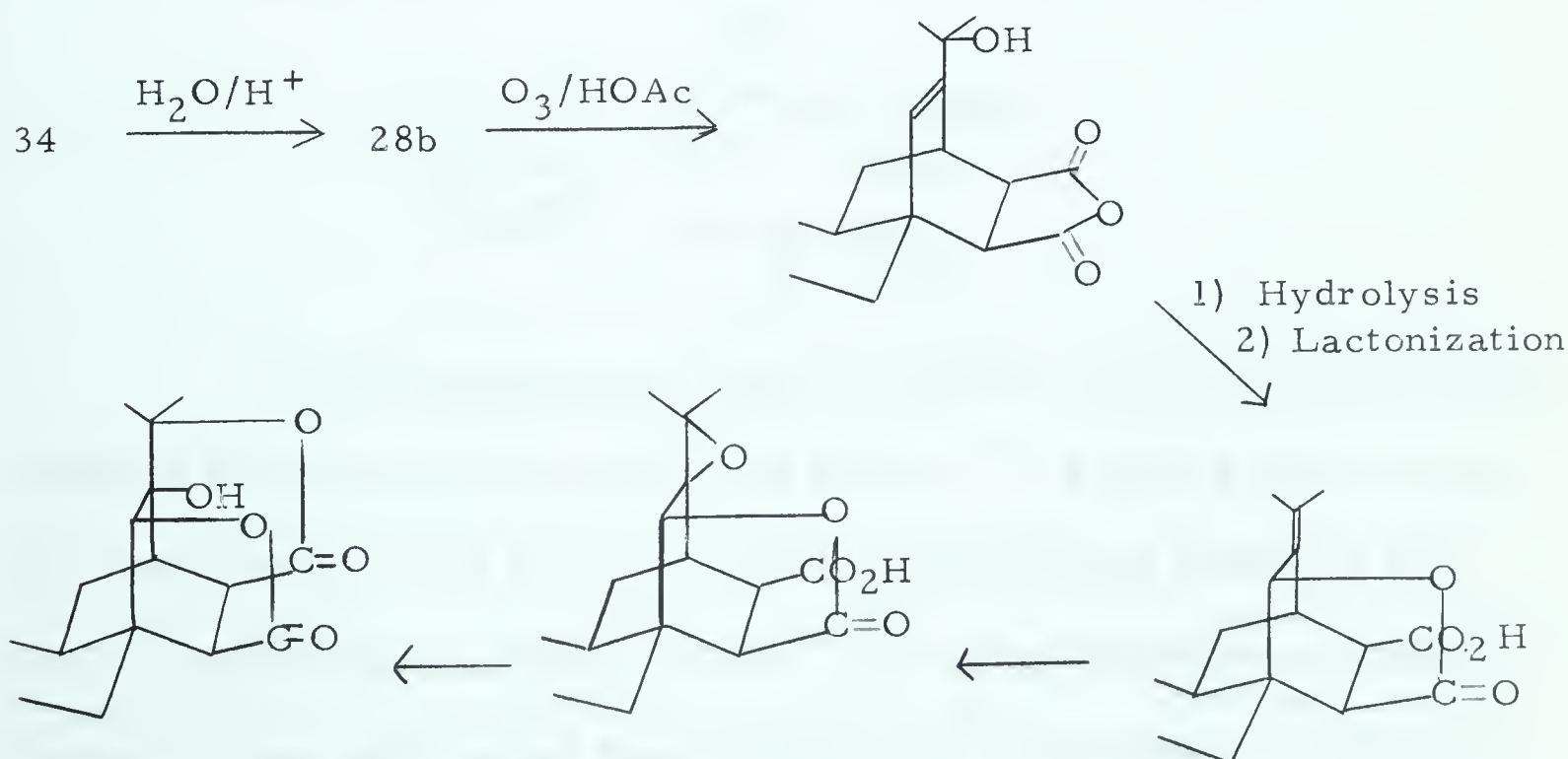
With this analogy in mind, formation of the methyl ketone 38 can be visualized in terms of an allylic oxidation by ozone at C-18 resulting in formation of an alkoxy radical which is then converted to the ketone either by the loss of a methyl radical or by conversion to the allylic alcohol 54 (see above).

Formation of the methyl ketone 38 can also be rationalized by the following ionic mechanism. In this representation, the cationic intermediate B can lead to both the methyl ketone 38 and the bicyclic ketone 59 by migration of either the methyl or the vinyl group.



The bicyclic ketone 59 may also arise by a Baeyer-Villiger oxidation of the methyl ketone 38, probably by peracetic acid formed through a slow oxidation of acetic acid by ozone⁷⁴ or less likely, by a direct attack of ozone at the carbonyl carbon with subsequent rearrangement and elimination of molecular oxygen[‡].

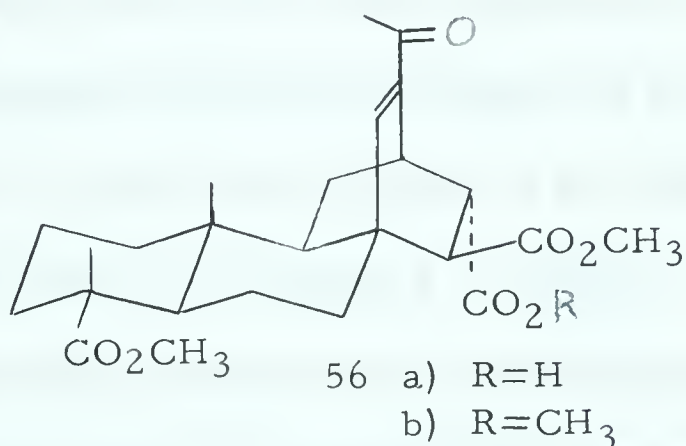
A concise and plausible reaction sequence rationalizing the transformation of the cis trimethyl ester 34 to the hydroxy dilactone 52 involves an initial hydrolysis of the C-21 and/or C-22 carbomethoxyl groups and formation of methyl maleopimarate which is then transformed by an allylic oxidation and rearrangement with concurrent lactonization to the unsaturated lactone C-15 ester 50c. Epoxidation of the isopropylidene group, followed by acetic acid catalyzed oxide ring opening and lactonization then leads to the hydroxy dilactone 52.



‡ A precedent for the Baeyer-Villiger oxidation with ozone is found in the suggested mechanism for the conversion of benzaldehyde to benzoic acid with O_3/N_2 (reference 111, page 980).

Postulation of the unsaturated lactone 50c as an intermediate ester is supported by the observation that the cis trimethyl³⁴ is transformed to methyl maleopimarate (28b) in high yield by acetic acid containing a catalytic amount of sulfuric acid and by the further observation that 50c is one of the products obtained from ozonolysis of methyl maleopimarate (28b)³⁷. The subsequent transformation leading to the hydroxy dilactone 52 finds an obvious parallel in the dimethyl ester series and requires no special comment.

The methyl ketone 38 was further characterized by saponification to the monoacid 56a, $C_{25}H_{34}O_7$, m.p. 230-31°C (reported 226-28°C) according to the published procedure⁴⁹.



The monocarboxylic acid formulation was confirmed by broad infrared absorption between 2500 and 3400 cm^{-1} , a strong carbonyl band at 1700-1730 cm^{-1} and by two 3 proton carbomethoxyl signals in the n.m.r. spectrum at 6.37 and 6.31 τ . The close resemblance which these chemical shift values bear to those of the monoacid 41 (6.30 and 6.37 τ) indicated that an epimerization and saponification of the C-21 ester function had occurred here also. Additional evidence supporting

this view was obtained by converting the monoacid 56a to the corresponding methyl ester 56b with diazomethane. The infrared spectrum of this oily triester showed carbonyl absorption at 1730 cm^{-1} (sh), 1720 (s) and 1660 cm^{-1} . The carbomethoxyl groups were characterized by signals at 6.38, 6.31 and 6.27τ in the n.m.r. spectrum. Disappearance of the characteristic infrared band at 1750 cm^{-1} and the similarity which the carbomethoxyl region of the n.m.r. spectrum bears to that of the trans trimethyl ester 32b (signals at 6.38, 6.31 and 6.27τ) are both consistent with a C-21 exo carbomethoxyl group. Chemical confirmation for a trans arrangement of the C-21 and C-22 carbomethoxyl groups was obtained by the isolation of dimethyl fumarate in ca. 20% yield on heating the trimethyl ester 56b under vacuum at $255-60^{\circ}\text{C}$ for 80 minutes.

Conversion of the methyl ketone 38 to the trans epimer 56b was accompanied by significant changes in the ABX coupling pattern displayed by the protons on carbons 6, 21 and 22. In the former case, the n.m.r. spectrum contained two 1 proton signals at 6.95τ and 7.12τ . The later peak appeared as a doublet with a line spacing of 11.0 c.p.s., while the former consisted of a pair of doublets with spacings of 11.0 and 1.7 c.p.s.. Since the steric requirements for long range coupling are not met by the C-6 and C-22 protons^{76,77}, the doublet at 7.12τ must represent the C-22 proton and the quartet at 6.95τ , which can now be assigned to the C-21 proton, therefore arises from an additional coupling with the bridgehead proton. The C-6 methine hydrogen could not be identified directly but was assigned a chemical shift value of 6.5τ

because the integral spectrum established the presence of 10 protons in the carbomethoxyl region.

In the trans epimer 56b, the C-6 hydrogen was represented by a broad multiplet at 6.6 τ , the C-22 proton by a clean doublet at 7.0 τ ($J_{AB} = 6.0$ c.p.s.) and the C-21 proton by a quartet ($J_{AB} = 6.0$; $J_{AX} = 3$ c.p.s.) centered at 7.5 τ .

The J_{AX} and J_{AB} coupling constants of the methyl ketone 38 were very similar in magnitude to those obtained from several other compounds possessing eclipsed C-21 and C-22 carbomethoxyl groups and is clearly different from the trans epimer 56b and the hydroxy trimethyl ester 44b, the only other C-21, C-22 trans compound thus far encountered on which an analysis was possible. The coupling constants for these compounds are listed in Table I.

TABLE I

Chemical Shifts and Coupling Constants of the C-6, C-21 and C-22 Protons.

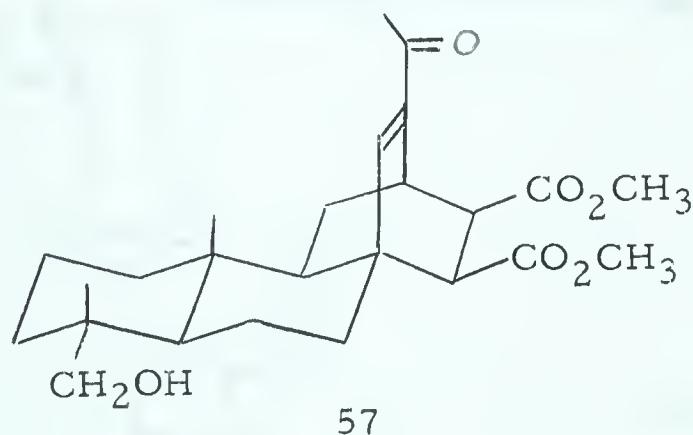
Compound	C-6H (X)	C-21H (A)	C-22H (B)	Configuration	J_{AB}	J_{AX}
50b	6.9	7.58	7.11	cis	10.1	1
51	7.8	7.5	7.0	cis	10.0	1
52	-	7.65	6.90	cis	10.0	-
56b	6.6	7.5	7.0	trans	6.0	3
44b	7.6	6.7	7.1	trans	4.0	4

The dependence of the extent of coupling between vicinyl protons on dihedral angle Θ in six membered rings is firmly established and has been shown to be at a maximum when $\Theta=0^\circ$ or 180° and at a minimum when $\Theta=90^\circ$ ⁷⁸. The decrease in J_{AB} observed when the C-21 carbomethoxyl group is epimerized to an exo position is therefore not surprising since the process increases the angle from 0° to 120° . However, although these variations of J_{AB} are in qualitative agreement with theoretical considerations, they are nonetheless both considerably larger than the predicted values. The reason for this, as well as for the larger J_{AX} coupling in compounds containing an exo C-21 carbomethoxyl group (44b and 56b) is not readily apparent.

Several attempts to reduce the olefinic bond of the methyl ketone 38 with lithium in tetrahydrofuran-liquid ammonia were unsuccessful, the reaction leading to reduction of the C-15 carbomethoxyl group and the formation of a considerable amount of acidic material. In one experiment the acidic portion of the product (ca. 30%) yielded, after esterification with diazomethane and chromatography on alumina, a small amount of impure starting material, m.p. $150-160^\circ\text{C}$, identified by infrared spectral comparison with authentic material. Chromatography of the neutral portion of the reaction product on alumina provided the C-1 hydroxymethyl ketone 57 as an impure oil which was identified by the following infrared and n.m.r. spectral properties.

The equatorial hydroxymethyl group at C-1 was identified by a sharp monomeric peak at $\nu_{\text{max}} 3638 \text{ cm}^{-1}$, broad hydrogen bonded

hydroxyl absorption at $3450-3550\text{ cm}^{-1}$ and by a three proton n.m.r. signal at 9.31τ , characteristic of the axial C-16 methyl group in this system (compare with the value of 9.24τ observed for the hydroxy anhydride 35 and dimethyl ester 36). Retention of the $\alpha\beta$ unsaturated ketone moiety was evident from a strong infrared band at 1670 cm^{-1} and a weak peak at 1615 cm^{-1} and from signals in the n.m.r. spectrum at 9.48τ (3H, C-17 protons) and 3.19τ (1H, olefinic H). The C-21 and C-22 endo carbomethoxyl groups were characterized by infrared absorption at 1750 cm^{-1} (shoulder) and n.m.r. signals at 6.53 and 6.51τ .



Formation of the acidic material can be accounted for by either a base catalyzed hydrolysis resulting from the presence of water in the solvent, or by an ether type reductive cleavage to the acid as has been previously encountered with hindered methyl esters in lithium-liquid ammonia systems⁷⁹. No attempt, however, was made to distinguish between these two possibilities or to identify the acidic product(s).

The Bouveault-Blanc type reduction of the methyl ketone 38 with lithium in tetrahydrofuran-liquid ammonia leading to formation of

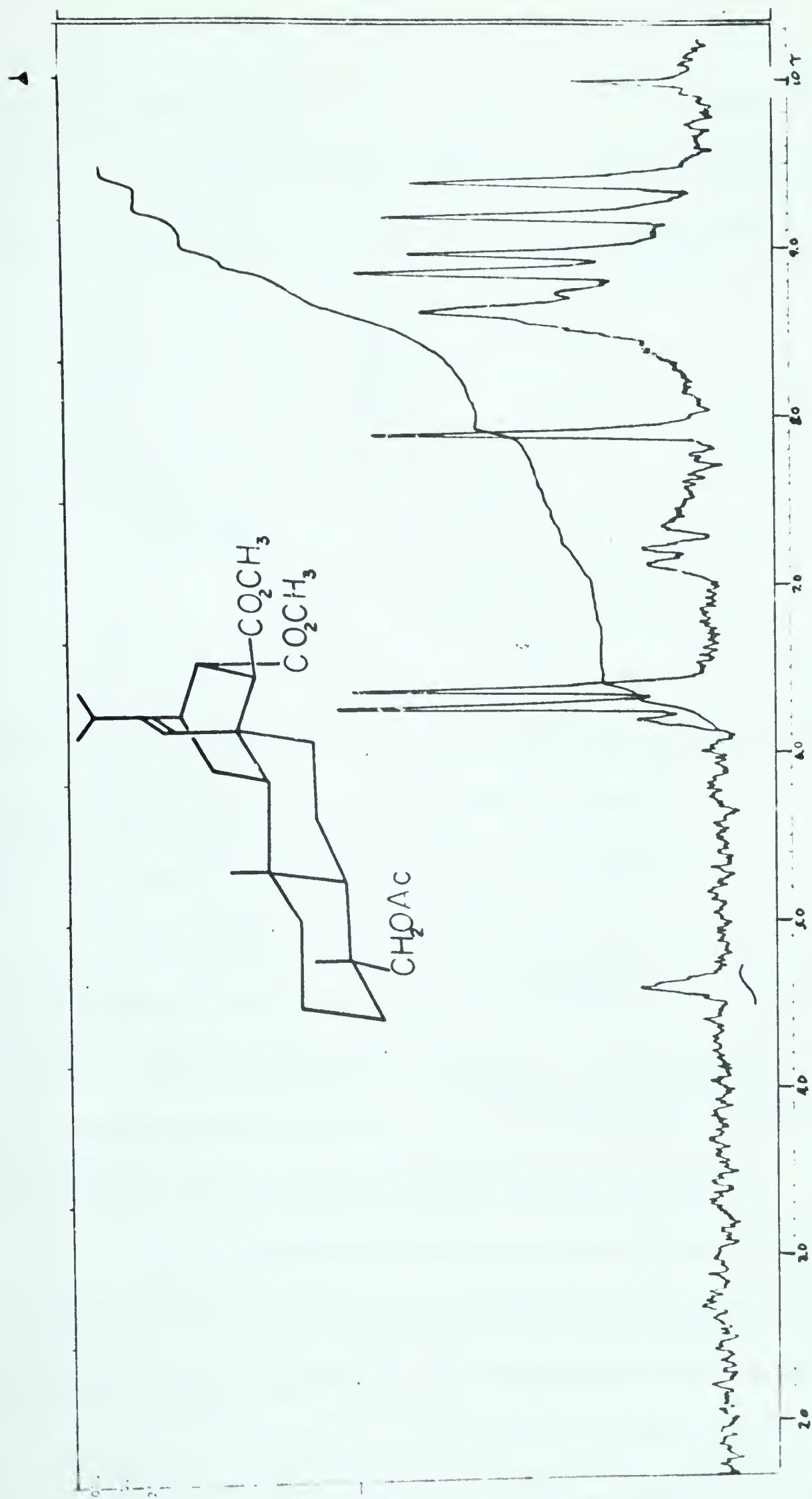
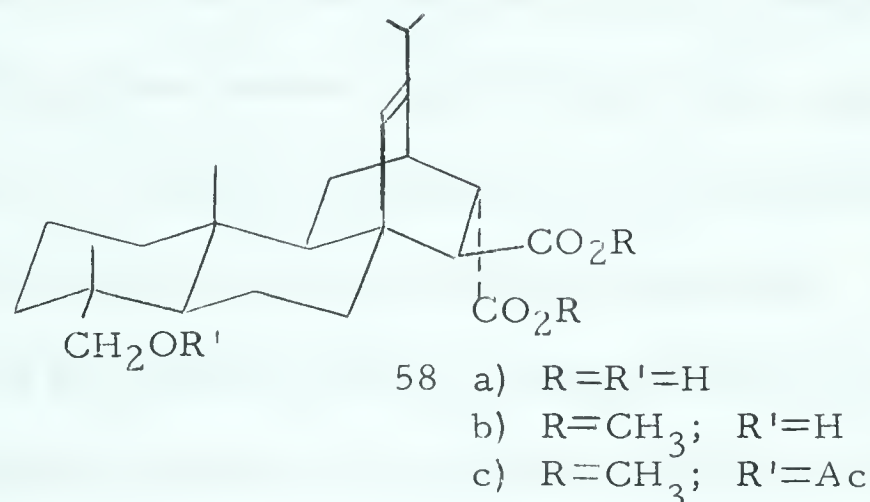


Figure 16. Nuclear magnetic resonance spectrum of the acetoxy methyl dimethyl ester 58c.

the hydroxymethyl ketone 57 has been observed previously in diterpene chemistry⁷⁹ and has also been applied successfully in reducing the diacid 42 to the hydroxymethyl diacid 58a, $C_{24}H_{36}O_5$, m.p. 258-63°.



The hydroxyl group was identified by absorption at $\checkmark_{\max}^{Nujol}$ 3462 (sharp) and 3380 (broad) cm^{-1} , while the carboxyl groups were characterized by broad hydrogen bonded absorption between 3300 and 2400 cm^{-1} and by a strong carbonyl band at 1705 cm^{-1} .

The hydroxymethyl diacid 58a was also prepared by saponifying the hydroxy dimethyl ester 36 with sodium hydroxide in aqueous methanol. The identity of the compounds was established by melting point and mixture melting point determination and by infrared spectral comparison of the corresponding oily dimethyl ester 58b.

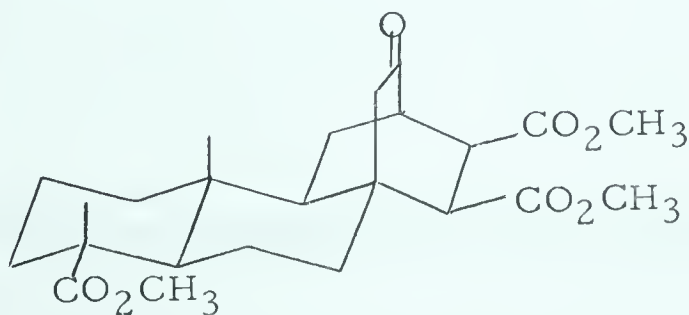
The equatorial C-1 hydroxymethyl group of the dimethyl ester 58b was identified by infrared absorption at 3640 cm^{-1} (s) and 3550 cm^{-1} (broad), and by a 3 proton signal at 9.25 τ in the n.m.r. spectrum readily assigned to the axial C-16 methyl group. The carboxymethoxyl functions were characterized by infrared absorption at 1725 cm^{-1} and by 3 proton n.m.r. signals at 6.37 τ (C-22 endo CO_2CH_3)

and 6.28τ (C-21 exo CO_2CH_3).

The dimethyl ester 58b was converted to the oily acetate 58c by room temperature acetylation with acetic anhydride in pyridine. The acetate group was identified by carbonyl absorption at ν_{max} 1740 cm^{-1} and by a three proton signal in the n.m.r. spectrum at 7.97τ . The axial C-17 protons resonated at 9.19τ , somewhat lower than encountered in the C-1 hydroxymethyl compounds. This small deshielding effect of the acetoxy group is consistent with its slightly greater electronegativity relative to the hydroxyl function (3.80 and 3.43 respectively)⁸⁰.

The difficulties encountered in attempting to reduce the carbon-carbon double bond of the methyl ketone 38 discouraged further attempts to effect a Baeyer-Villiger oxidation on the saturated ketone and attention was therefore turned towards the application of this reaction to the methyl ketone 38 itself.

Room temperature oxidation of a tetrahydrofuran solution of the methyl ketone 38 with 90% hydrogen peroxide in boron trifluoride etherate⁸¹ was found to provide directly the bicyclic ketone 59, $\text{C}_{24}\text{H}_{34}\text{O}_7$, m.p. $195-6^\circ$, in 45-50% yield.



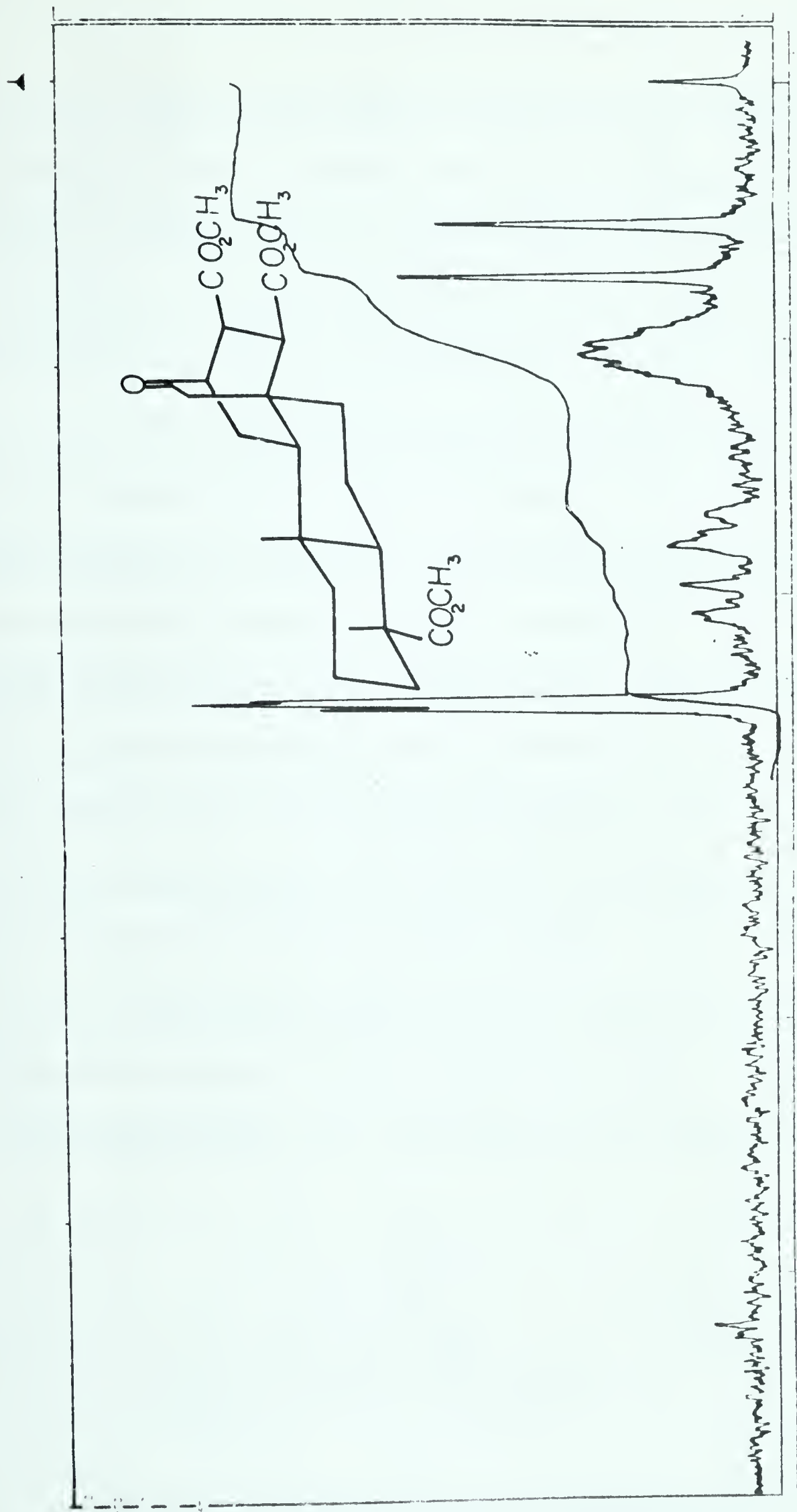
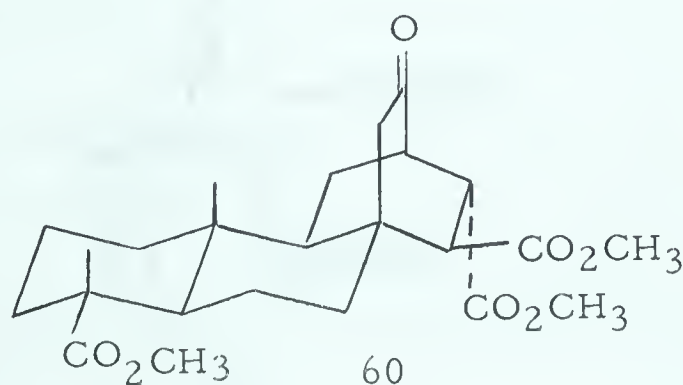


Figure 17. Nuclear magnetic resonance spectrum of the bicyclic ketone 59.

The C-7 keto function was identified by ultraviolet absorption at $284\text{ m}\mu$ ($\epsilon = 28$), a negative Cotton effect ($[\alpha]_{300} -945^\circ$ (trough) $[\alpha]_{265} +139^\circ$ (peak)) and a medium intensity infrared band at 1410 cm^{-1} , resulting from a displacement of the C-8 methylene scissoring vibration from its normal value of $\text{ca. } 1470\text{ cm}^{-1}$ by the adjacent carbonyl group⁸².

The C-16 methyl group was identified by the characteristic 3 proton signal at 8.86τ while the angular methyl at C-12, showing approximately the same extent of shielding by the carbonyl group as was observed for the isopropylidene compounds 45 and 50b (9.18 and 9.26τ respectively), was located at 9.16τ . The eclipsed C-21 and C-22 carbomethoxyl groups were represented by n.m.r. absorption at 6.37τ and 6.40τ and by infrared absorption at 1750 cm^{-1} . A second carbonyl band at $1720\text{-}1730\text{ cm}^{-1}$ was assigned to the 7-keto function and the two remaining ester groups.

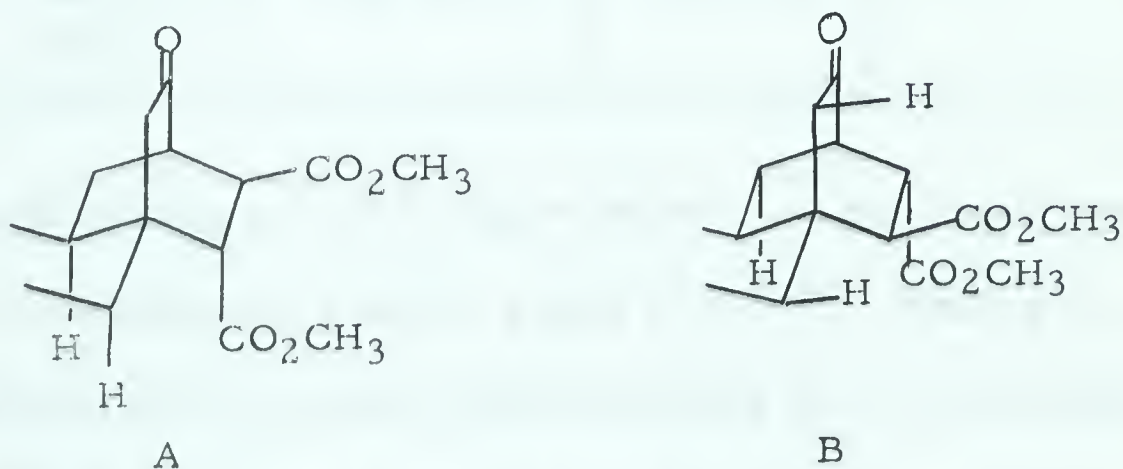
The bicyclic ketone 59 was further characterized by conversion to the trans trimethyl ester 60, $\text{C}_{24}\text{H}_{34}\text{O}_7$, m.p. $150\text{-}150.5^\circ\text{C}$, through saponification and reesterification with diazomethane.



A trans relationship of the C-21 and C-22 carbomethoxyl groups was indicated by the infrared spectrum which contained a single

broad carbonyl band at $1720-1732\text{ cm}^{-1}$, the high frequency band at $\text{ca. } 1750\text{ cm}^{-1}$, characterizing the eclipsed configuration, being absent. This assignment was confirmed by the n.m.r. spectrum which showed a 7.5 c.p.s. coupling between the protons on carbons 21 and 22 as well as a downfield shift of the C-21 and C-22 carbomethoxyl protons to 6.31τ and 6.27τ .

The question of whether epimerization had occurred at C-21 or C-22 is of some interest since, if the reaction conditions permit equilibration, the expected product is the C-22 exo epimer (part structure A). This conclusion can be arrived at by assuming that the relative stabilities of the two possible trans epimers are determined by the 1,3 hydrogen-carbomethoxyl diaxial interactions. The C-22 exo and endo configurations should be of equal stability since both contain two such interactions, but the C-21 exo epimer should be destabilized relative to the endo alternative by the 1,3 interaction with the axial C-5 hydrogen (part structure B).



If, on the other hand, the epimerization is under kinetic control, the expected product is the C-21 exo epimer because, as

mentioned earlier, proton abstraction and hence enolization should be more facile at C-21 than at C-22. Inasmuch as there was no direct experimental evidence bearing on the relative importance of kinetic and thermodynamic factors in the previous saponifications it was necessary to obtain experimental confirmation for the presence of a C-21 exo carbo-methoxyl group in the keto trans trimethyl ester 60. With this objective in mind the 7τ region of the n.m.r. spectrum was examined with the aid of spin decoupling techniques. The results are summarized in Table II.

TABLE II

The 7τ Region of the Keto Trans Trimethyl Ester 60.

Proton	A	B	C	D
Chemical Shift	6.79 (1H)	7.11 (1H)	7.24 (1H)	7.59 (2H)
Multiplicity	Two triplets	Broad doublet	Quartet	Singlet
J-value (c.p.s.)	$J_{AC}=1.7$ $J_{AB}=7.5$ $J_{AX}=1.7$	$J_{AB}=7.5$ $J_{BD} < 0 < 1.2$	$J_{CY}=5$ $J_{AC}=2.0$	.

The broad doublet at 7.11τ (half width = 2.4 c.p.s.) narrowed to 1.2 c.p.s. on irradiating the 2 proton signal at 7.54τ . Making the reasonable assumption that the latter peak represents the C-8 methylene group, this observation indicates a coupling with the C-22 proton which, in order to meet the steric requirements for long range coupling, must be exo orientated. The additional large coupling of 7.5 c.p.s. with H_A ,

together with the other evidence for trans C-21 and C-22 substituents , thus enables the assignment of a C-21 exo carbomethoxyl group to the keto trans trimethyl ester 60. The further splitting shown by H_A is due , in part , to a small coupling with the bridgehead methine (H_C) , confirmed by the appropriate double irradiation experiment and probably to a long range coupling with the equatorial C-5 proton. The reason for the unusually small coupling between H_C and H_A , which is also observed in other trans compounds derived from the bicyclic ketone 59 (cf. compounds 82 and 84b) , and is in distinct contrast to the 4-6 c.p.s. couplings observed for trans compounds in the isopropyl series , is not understood.

The ready availability of the bicyclic ketones 59 and 60 led to speculation on the possibility of oxygenating C-17 by first reducing the ketone to a secondary alcohol and then reacting this with lead tetraacetate in the hope of forming an ether bridge between C-7 and C-17⁸³. Oxide ring opening with boron trifluoride in acetic anhydride followed by removal of the oxygen function at C-7 would then permit a correlation with the atisine derivative 25a (page 8) or the corresponding acid 25b.

Although this reaction sequence was never developed it did result in several attempts to prepare the secondary alcohol necessary for the important ring closure reaction. Since the model compound employed in these studies was the keto trans triester 60 the experiments will now be described briefly.

Reduction of the keto trimethyl ester 60 with aluminum isopropoxide in boiling isopropanol provided the secondary alcohol in 95% yield



Figure 18. Infrared spectrum of the hydroxy trimethyl ester 61.

spectrum. The hydroxy trimethyl ester 61, however, despite an identical arrangement of carbomethoxy groups, showed both bonded and non-bonded hydroxyl absorption and no abnormally low ester carbonyl band. An obvious explanation for this difference in spectral properties is that the hydroxyl group in the reduction product is trans to the C-21, C-22 bridge and therefore incapable of being intramolecularly hydrogen bonded.

This assignment is supported by the n.m.r. spectrum of the hydroxy trimethyl ester 61 which showed a signal at 8.92 τ due to the C-17 protons. This value is, with one exception (the thioketal 86, page 183), 0.12-0.13 p.p.m. lower than the resonance position observed for the angular methyl in other compounds encountered in this work. The paramagnetic shift is readily explained by the proposed structure since protons are known to be deshielded by nearby oxygen atoms.

Reduction of the keto trimethyl ester 60 with sodium borohydride in methanol containing added sodium hydroxide yielded an oily reduction product which, on reesterification with diazomethane, showed two spots on t.l.c. analysis. Acetylation with acetic anhydride in pyridine provided a mixture of acetates identified by n.m.r. signals at 7.96 and 8.00 τ .

IV. PREPARATION OF THE C-1 GEM DIMETHYL ADDUCT 30.

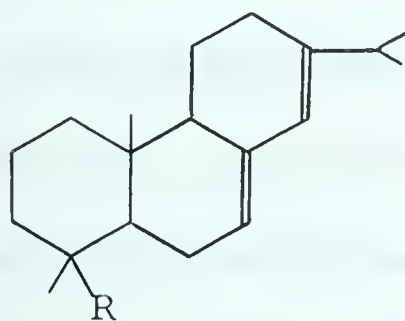
CORRELATION OF THE RESIN ACIDS WITH ATISINE.

Concurrent with these efforts to degrade the isopropyl side-

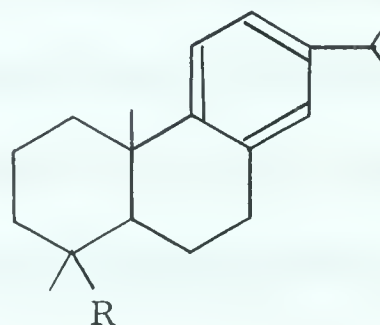
chain of maleopimaric acid, an attempt was also being made to extend the maleic anhydride Diels-Alder reaction to abieta-7,14(9)-diene.

The results of these studies are described in the following paragraphs.

The nuclear magnetic resonance spectrum of commercial methyl abietate 27b showed the expected⁴² absorption at 9.19 τ (C-17 methyl), 9.00 τ ($J = 6.5$) (isopropyl methyls), 8.84 τ (C-16 methyl), 6.39 τ (carbomethoxyl) and 4.3-4.8 τ (vinyl protons). In addition, however, the spectrum contained strong absorption at 8.76 τ and aromatic signals at 3.02, 3.11 and 3.25 τ . These signals are most readily accounted for in terms of a ring C aromatization leading to formation of methyl dehydroabietate (62a), and in fact the signals in the aromatic region compares favorably with those reported for the compound (3.04, 3.15 and 3.28 τ)⁴². On the basis of this interpretation the 8.76 τ signal can be assigned to the low field component of the isopropyl doublet attached to the aromatic ring.



- 27 a) $R = \text{CO}_2\text{H}$
 b) $R = \text{CO}_2\text{CH}_3$
 c) $R = \text{CH}_2\text{OH}$
 d) $R = \text{CHO}$
 e) $R = \text{CH}_3$



- 62 a) $R = \text{CO}_2\text{CH}_3$
 b) $R = \text{CH}_2\text{OH}$
 c) $R = \text{CHO}$
 d) $R = \text{CH}_3$

From the integral curve of the aromatic region it is concluded that the commercial preparation of methyl abietate is contaminated by

ca. 25% of methyl dehydroabietate (62a).

Reduction of methyl abietate (27b) with lithium aluminum hydride in anhydrous ether provided the crude abietinol (27c) in 90% yield as a viscous amber coloured oil ($\nu_{\max}$ 3640 cm^{-1}).

The C-16 and C-17 methyl groups were characterized by a strong n.m.r. signal at 9.18 τ , while the isopropyl group appeared as a doublet at 9.00 τ ($J=6.5$ c.p.s.). The diamagnetic shift of the C-16 protons accompanying reduction of the C-15 carbomethoxyl group is comparable with that encountered in previous examples (see page 66). The aromatic alcohol 62b was identified by an isopropyl doublet at 8.78 τ ($J=7$ c.p.s.) and broad absorption between 3.0 τ and 3.3 τ and, from the ratio of integrated absorption values for the aromatic and olefinic region (0.44), was estimated to be present to the extent of ca. 30%.

The mixture of alcohols was then oxidized to aldehydes 27d and 62 c with chromium trioxide in pyridine⁸⁴. The aldehyde functions were represented in the infrared spectrum by medium intensity absorption at 2695 and 2685 cm^{-1} and by a strong carbonyl band at 1725 cm^{-1} . The n.m.r. spectrum contained signals at 0.85 τ and 1.45 τ in an intensity ratio of 1:2, which are assigned to the formyl hydrogen of the aromatic aldehyde 62c and abietinal (27d) respectively.

The aldehyde mixture was then treated with methanolic semicarbazide and the semicarbazone, which immediately precipitated from solution in ca. 40% yield, recrystallized several times from ethyl acetate. The purified sample, m.p. 207-214°C, (reported⁸⁵ 215°C) possessed the

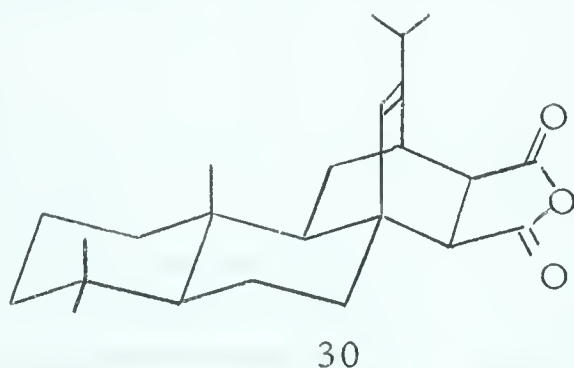
expected ultraviolet absorption at $234\text{ m}\mu^{86}$ and showed infrared maxima at 3537 cm^{-1} and 3413 cm^{-1} representing the asymmetrical and symmetrical N-H stretching vibrations. The amide I and amide II vibrations appeared as strong absorption bands at 1685 and 1570 cm^{-1} .

Wolff-Kishner reduction of the semicarbazone in diethylene glycol solution at 190° provided a mixture of abieta-7,14(9)-diene (27e) and the corresponding aromatic hydrocarbon 62d in greater than 90% yield. The purified product, obtained by vacuum distillation at $130\text{--}150^\circ\text{C}$ ($0.05\text{--}0.10\text{ mm.}$), showed C-methyl absorption in the n.m.r. spectrum at 9.22 , 9.12 and 9.06τ , assigned to the C-12 angular methyl and the C-1 gem dimethyl groups respectively. The isopropyl methyls appeared as a doublet centered at 9.00τ ($J=6.5\text{ c.p.s.}$) and the two vinyl protons as signals at 4.31τ and 4.70τ . The low field signal which appeared as a sharp singlet can be assigned to the C-8 hydrogen while the broad peak at 4.70τ is assigned to the C-10 proton which has an adjacent methylene group. The aromatic impurity (62d) was indicated by an isopropyl doublet at 8.79τ ($J=6\text{ c.p.s.}$) and by absorption at 3.02 , 3.12 and 3.26τ . From the integrated absorption values of the aromatic and olefinic regions it was concluded that the hydrocarbon mixture contained ca. 62% abieta-7,14(9)-diene.

In an alternate sequence, commercially available rosin was reduced with lithium aluminum hydride to a mixture of abietinol and the corresponding aromatic alcohol 62b in 63% yield. This was then oxidized as before to the crude abietinal with Sarett's reagent and the derived

semicarbazone converted via a Wolff-Kishner reduction to the oily hydrocarbon mixture (27e and 62d). Integration of the aromatic and olefinic region indicated that the mixture contained 84% abieta-7,14(9)-diene.

When this latter preparation of abieta-7,14(9)-diene was heated with maleic anhydride in a sealed tube at 160° for 8 hours and the crude product subjected to chromatography on silica gel, a 14% yield of the gem dimethyl anhydride 30, $C_{24}H_{34}O_3$, m.p. 110, was obtained.



The infrared spectrum showed the characteristic anhydride absorption at 1850 and 1770 cm^{-1} and a weak olefinic stretching vibration at 1635 cm^{-1} .

The n.m.r. spectrum showed the C-8 vinyl proton signal at 4.41τ and a high field peak at 9.42τ assigned to the shielded angular methyl at C-12. The isopropyl group appeared as a doublet at 8.99τ ($J = 7\text{ c.p.s.}$) and the C-1 gem dimethyl group as three proton singlets at 9.18 and 9.09τ .

The Diels-Alder adduct 30 was further characterized by conversion to the dimethyl ester 63, m.p. $124-25^{\circ}\text{C}$, with methanolic

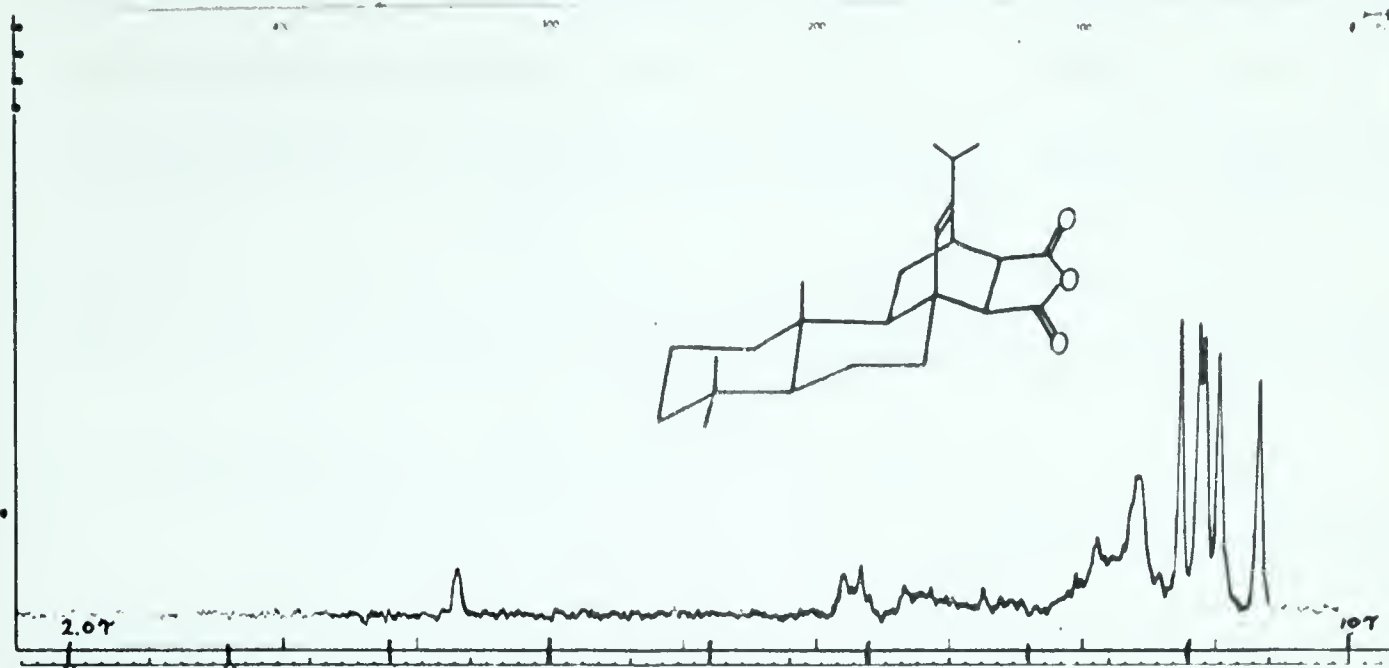


Figure 19. Nuclear magnetic resonance spectrum of the gem dimethyl anhydride 30.

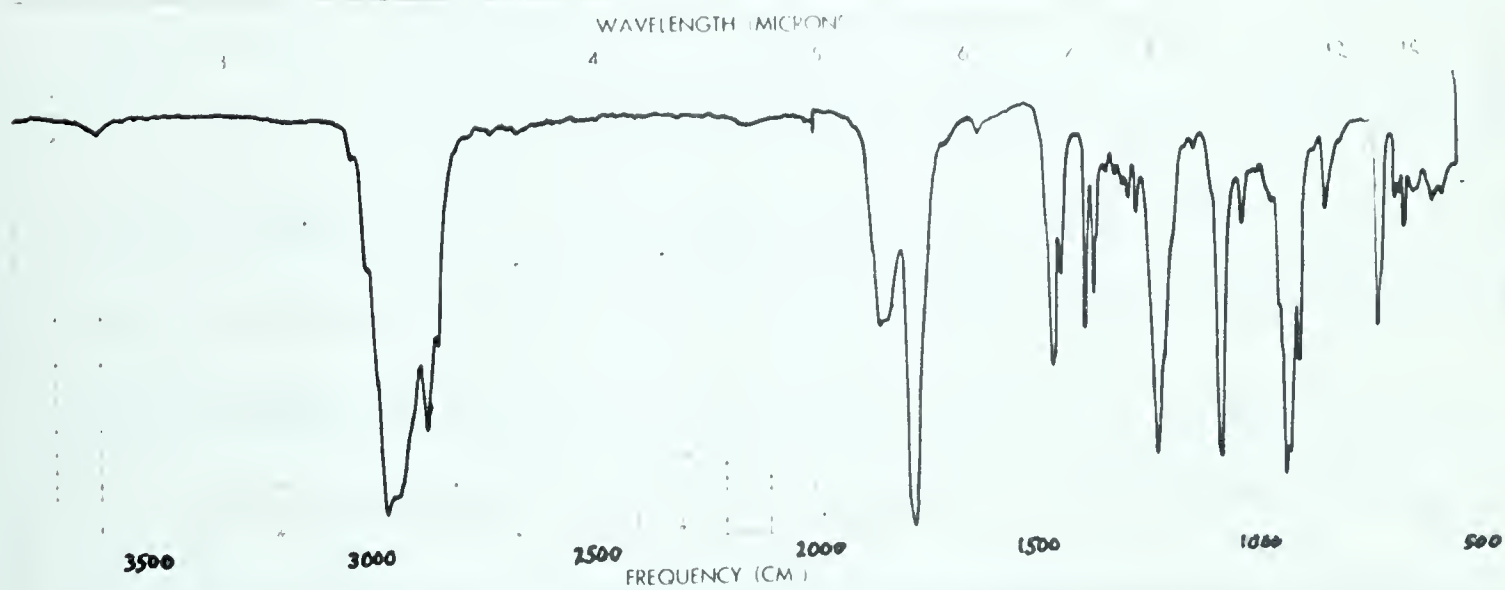


Figure 64. Infrared spectrum of the gem dimethyl anhydride 30.

diazomethane. The eclipsed C-21 and C-22 carbomethoxy functions were identified by a six proton signal at 6.47 τ and by the 10 c.p.s. coupling of the α C-21 and C-22 hydrogens. The C-1 gem dimethyl group was represented by 3 proton signals at 9.19 and 9.13 τ , while the isopropyl methyls, found to be slightly non-equivalent, appeared as doublets at 8.91 and 8.95 τ ($J=7$ c.p.s.).

It is interesting to note that, of the compounds discussed to this point, the only other examples of non-equivalence were encountered in the cis trimethyl ester 34 (8.91 and 8.95 τ), the hydroxymethyl diester 36 (8.90 and 8.94 τ) and the exo methylene dimethyl ester 47 (8.91 and 8.95 τ).

It has been known for some time that the protons of a methylene or isopropyl group, situated near a center of molecular asymmetry, can be magnetically nonequivalent and display AB type n.m.r. spectra¹¹². The cause of this nonequivalence has generally been considered to be the existence of preferred conformations of these groups with respect to the asymmetric center although it has been pointed out that there may exist an intrinsic asymmetry capable of causing the observed chemical shift differences even in the absence of hindered rotation¹¹³. At the present time, however, there does not appear to be any convincing experimental evidence bearing on the problem of the possible importance of small contributions to magnetic nonequivalence arising from an intrinsic asymmetry, although recently an n.m.r. study on a series of 17 ortho- or meta- substituted N,N-di-

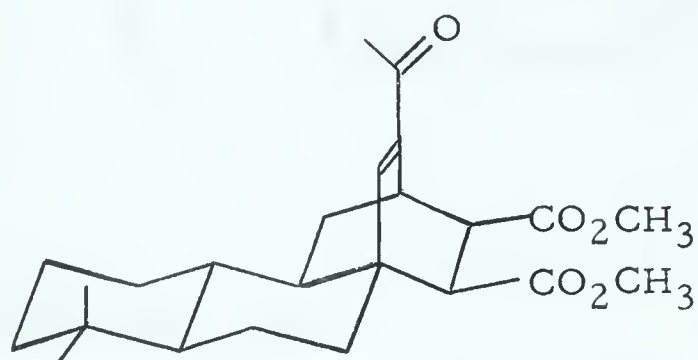
methylbenzylamine has indicated a long range effect of an asymmetric group in the ortho- or meta- sidechain on the magnetic equivalence of the methylene group protons in the amine side chain which may be due to non-steric factors¹¹⁴.

In the light of present knowledge, the observed nonequivalence of the isopropyl methyls in the cis methyl esters 34, 36, 47 and 63 would appear to be best explained in terms of a restricted rotation about the C-7, C-18 bond resulting from non-bonded interaction with the endo C-21 carbomethoxyl group, conditioned by the possibility that a portion of the observed nonequivalence may arise from an intrinsic asymmetry term¹¹⁵.

In later Diels - Alder experiments, employing the hydrocarbon mixture prepared from commercial methyl abietate, the addition was effected by heating the reactants at 150° for several hours in a stoppered round bottom flask. The crude product was then dissolved in benzene and converted to the insoluble sodium salt with aqueous sodium hydroxide. The purified salt, obtained in a 10% overall yield by recrystallization from tetrahydrofuran, was converted directly to the dimethyl ester 63 either by stirring at room temperature with dimethyl sulfate in methanol or by refluxing with a solution of HCl in anhydrous methanol. The crude dimethyl ester 63 obtained by esterification with dimethyl sulfate contained an undetermined amount of anhydride 30 ($\nu_{\text{max}}^{\text{CCl}_4}$ 1840 and 1770 cm^{-1}) and was generally treated with methanolic diazomethane prior to purification. The yields of diester 63 using this two step esterification

procedure, were in the order of 55-75%, somewhat lower than those realized (ca. 80%) with the Fisher esterification.

The dimethyl ester 63 was ozonized in the manner described for converting the cis dimethyl ester 34 to the methyl ketone 38 and the C-1 gem dimethyl ketone 64, $C_{25}H_{36}O_5$, m.p. 167-68°, isolated in ca. 30% yield via the Girard T derivative.



64

The conjugated carbonyl chromophore was indicated by ultra-violet absorption at 310 $m\mu$ ($\epsilon=43$) and 240 $m\mu$ ($\epsilon=9,600$) and by strong infrared absorption at 1662 cm^{-1} . The trisubstituted olefinic bond was characterized by a weak band at 1610 cm^{-1} and a one proton signal at 3.07 τ in the n.m.r. spectrum. The methyl ketone was characterized by a three proton n.m.r. signal at 7.63 τ , while the C-17 methyl group, showing the same enhanced shielding observed in the methyl ketone 38, appeared at 9.51 τ . This similarity also extended to the shielding pattern of the C-21 and C-22 carbomethoxyl groups, which were again chemically non-equivalent to the extent of 0.06 p.p.m.. The degree of shielding also compared favorably with the C-15 carbomethoxyl analog 38, judging from a comparison of the relevant chemical shift values (6.48 and 6.42 τ for the compound 64; 6.51 and 6.45 τ for compound compound 38).

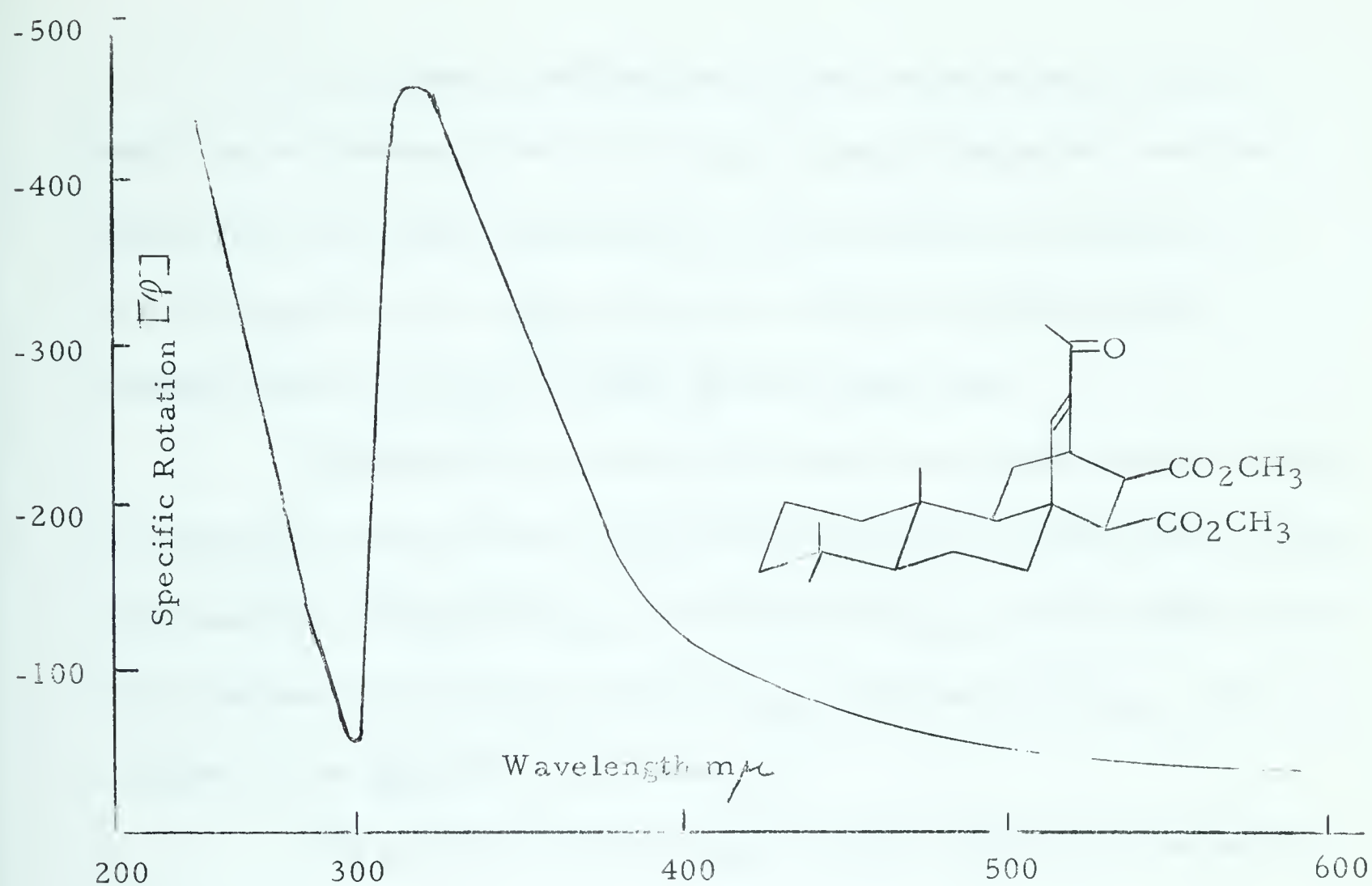


Figure 20. R.D. Curve of the Gem Dimethyl Ketone 64

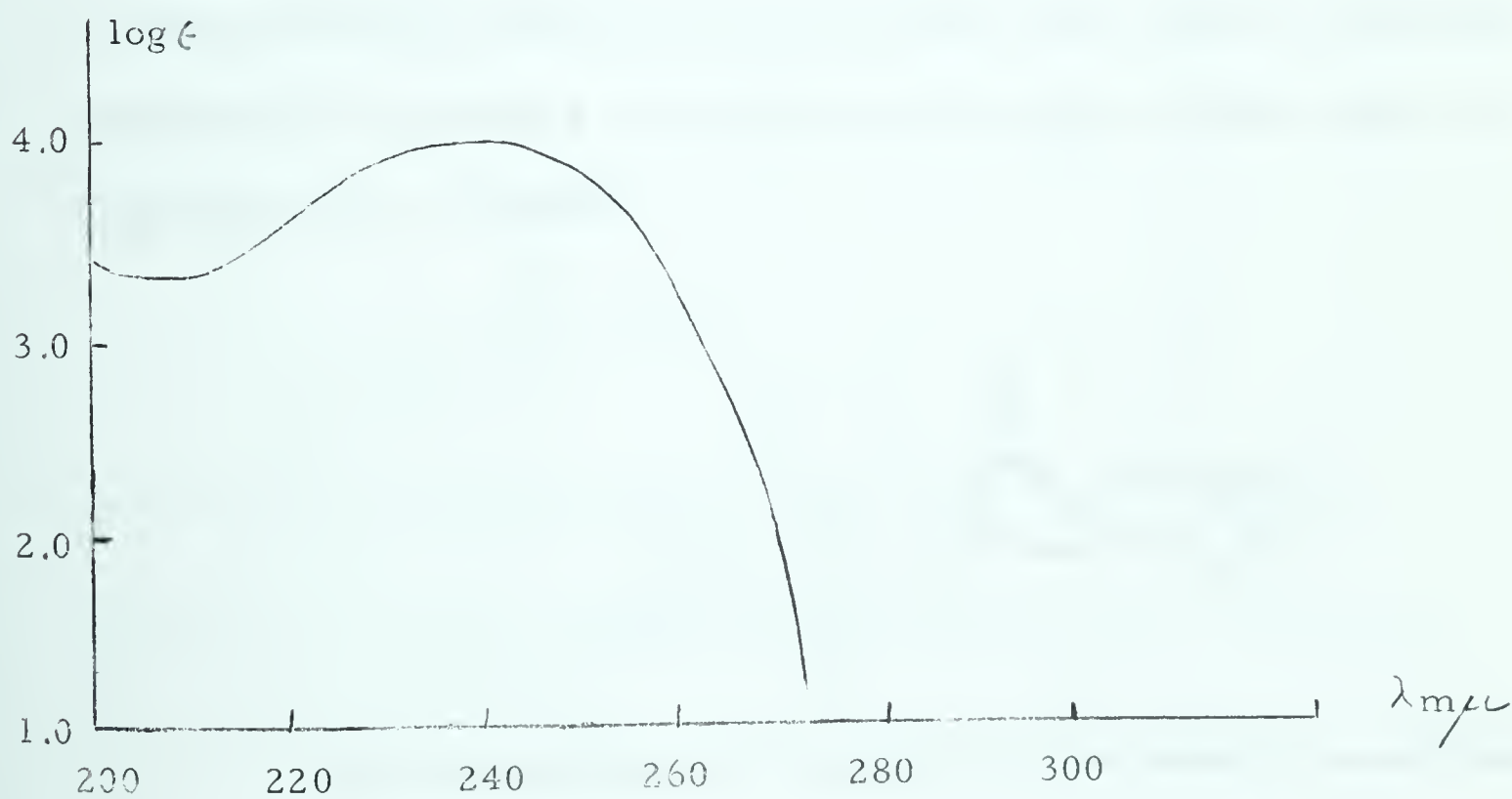


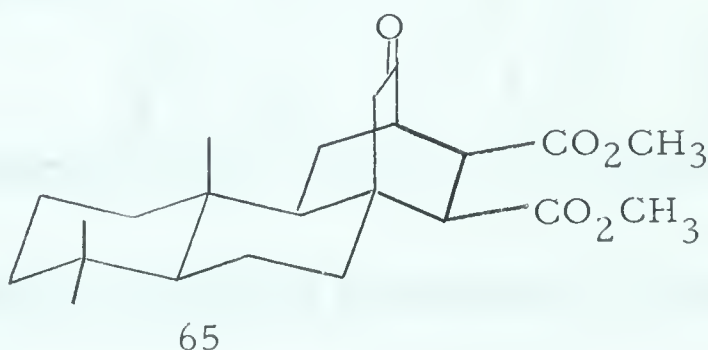
Figure 21. U.V. Spectrum of the Gem Dimethyl Ketone 64

An eclipsed configuration for the carbomethoxyl function, which can be deduced from the τ -values already discussed, was also indicated by the ABX coupling pattern of the protons on carbons 6, 21 and 22 ($J_{AB}=11$ c.p.s., $J_{AX}=2$ c.p.s.) and by the high frequency carbonyl band at 1745 cm^{-1} in the infrared spectrum.

A final point of similarity between the methyl ketones 38 and 64 was found in the fact that both possessed positive Cotton effect curves with maxima at $330\text{ m}\mu$ ($[\alpha]_{330} +318^\circ$ (peak); $[\alpha]_{290} +21^\circ$ (trough) for the C-15 carbomethoxyl analog 38 and $[\alpha]_{330} +460^\circ$ (peak); $[\alpha]_{287} +52^\circ$ (trough) for the gem dimethyl ketone 64).

The presence of a C-1 gem dimethyl group in the ketone 64 was established by three proton signals at 9.20 and 9.11 τ .

Oxidation of the methyl ketone 64 with 90% hydrogen peroxide in boron trifluoride-etherate by the procedure described for preparing the ketone 59, provided a 45% yield of the C-1 gem dimethyl ketone 65, $\text{C}_{23}\text{H}_{35}\text{O}_5$, m.p. $179-80^\circ\text{C}$.



The keto function was identified by low intensity $n \rightarrow \pi^*$ absorption at $284\text{ m}\mu$ ($\epsilon=28$) and by a negative Cotton effect curve, $[\alpha]_{298} -940^\circ$ (trough), $[\alpha]_{265} +281^\circ$ (peak) both of which showed a close correspondence

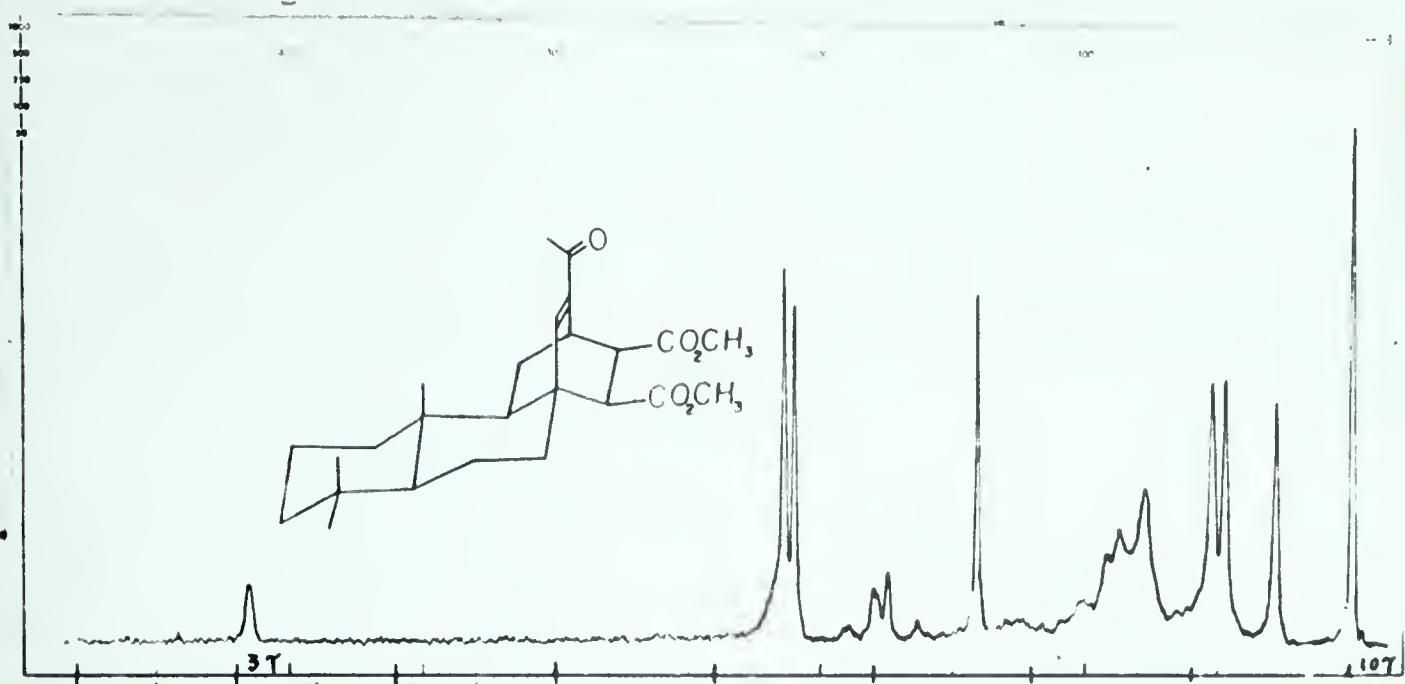


Figure 22. Nuclear magnetic resonance spectrum of the methyl ketone 64.

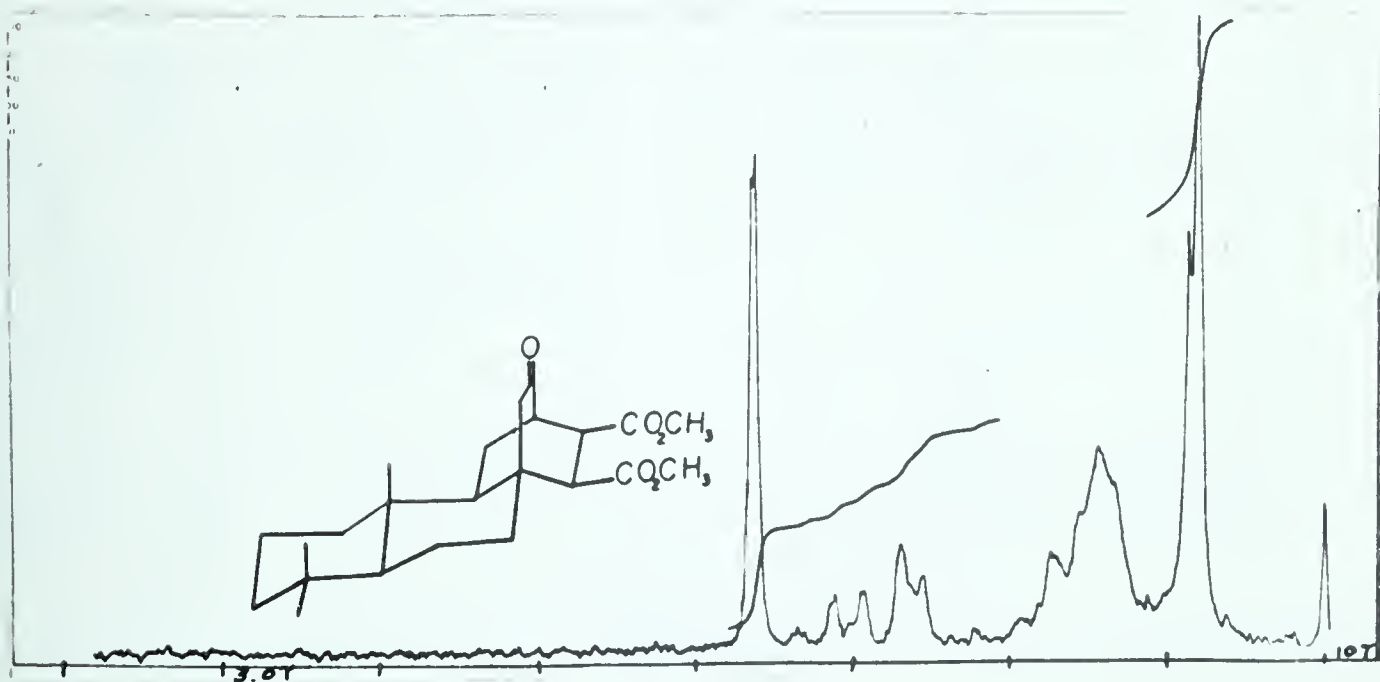


Figure 23. Nuclear magnetic resonance spectrum of the bicyclic ketone 65.

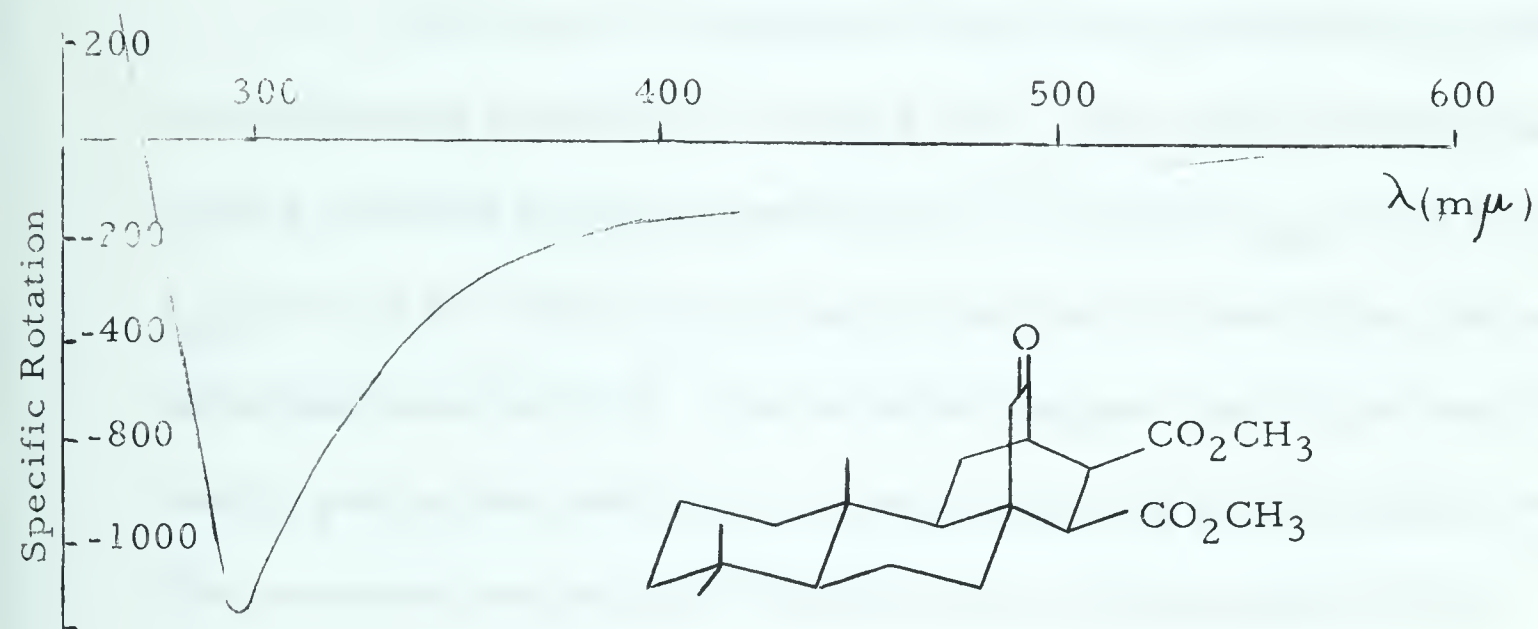


Figure 24. R.D. Curve of the Bicyclic Ketone 65

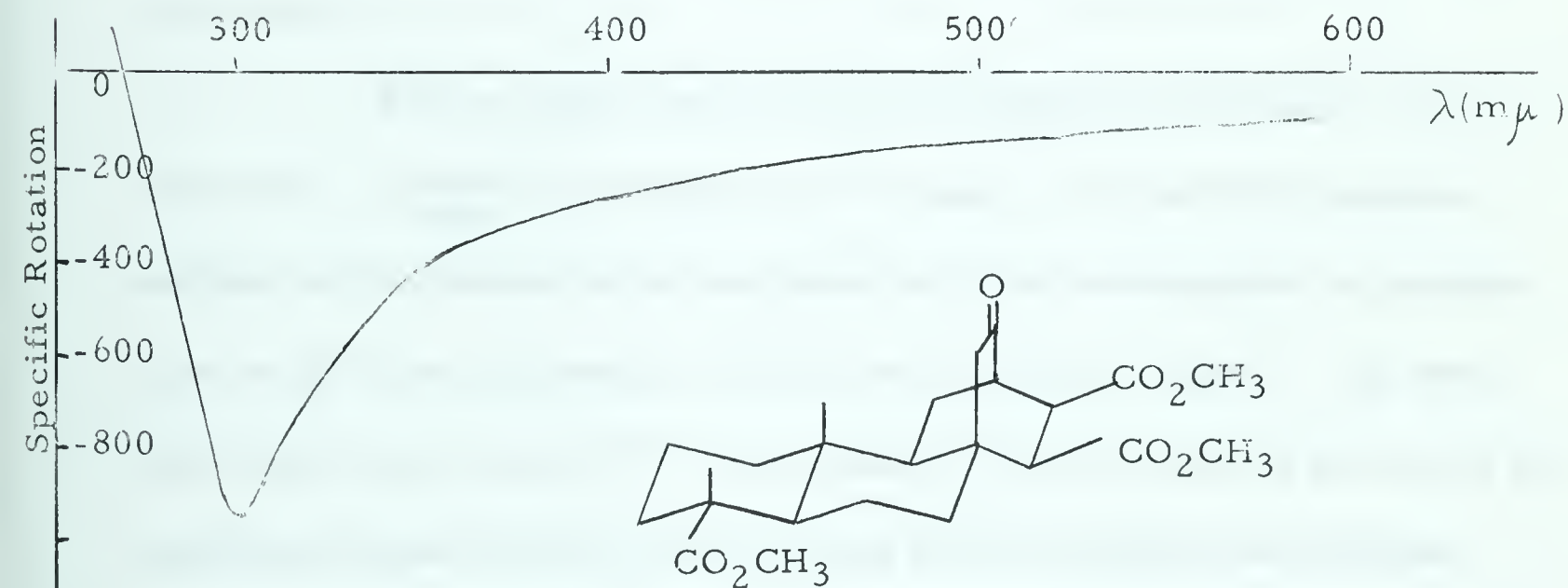


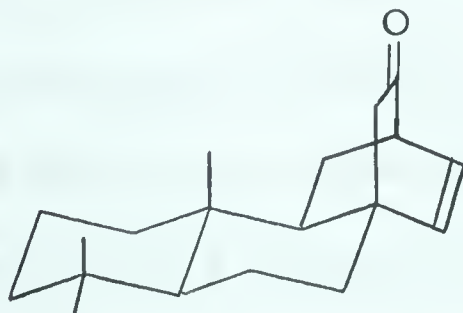
Figure 25. R.D. Curve of the Bicyclic Ketone 59

with the ultraviolet and rotatory dispersion characteristics of the ketone 59 (see page 71).

The n.m.r. spectrum showed the expected three proton carbomethoxyl signals at 6.35 and 6.38 τ , and an ABX coupling pattern arising from the protons on carbons 6, 21 and 22 ($J_{AB}=11.5$ c.p.s., $J_{AX}=2$ c.p.s.) which was partially obscured by absorption due to the methylene group at C-8. The shielded angular methyl and one of the methyl groups attached to C-1 appeared as a six proton signal at 9.17 τ . The remaining methyl was identified by a 3 proton peak 9.12 τ .

The C-8 methylene group was identified by a medium intensity infrared band at 1410 cm^{-1} and the eclipsed C-21 and C-22 carbomethoxyl groups by the characteristic high frequency ester carbonyl absorption at 1750 cm^{-1} .

The bicyclic ketone 65 was saponified to the diacid, m.p. 265-80°C ($\nu_{\text{max}}^{\text{nujol}}$ 3100-2400 cm^{-1} (broad), 1710 (s)) with aqueous sodium hydroxide and decarboxylated with lead tetraacetate in pyridine, first at 28°C for 30 minutes, then at 40-45°C for 5 hours. The keto olefin 66, m.p. 123-23.5°C, was isolated from the neutral portion of the reaction product in low yield following chromatography on alumina.



The C-21 and C-22 vinyl hydrogens, which formed part of an ABX coupling system with the bridgehead methine (represented by a broad multiplet at 6.98 τ), appeared as quartets at 3.95 and 3.81 τ respectively ($J_{AB}=8$ c.p.s., $J_{AX}=6$ c.p.s., $J_{BX}=2$ c.p.s.).

Recently, attention has been focused on the importance of ring size in determining the extent of coupling between the olefinic protons in cycloalkenes^{87,88,89}. Relevant to the present discussion are the ranges of coupling constants established for cyclopentenenes ($J=5.4-7.0$ c.p.s.), cyclohexenes ($J=8.8-10.5$ c.p.s.) and cycloheptenes ($J=9.7-12.5$ c.p.s.).

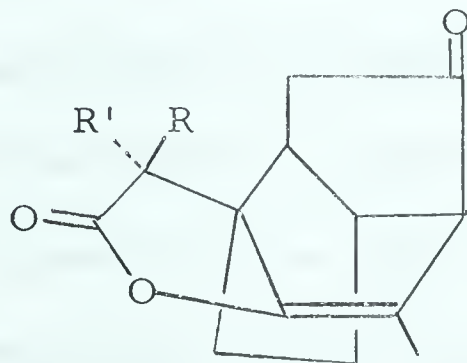
In bicyclic systems the coupling constants for numerous norbornene derivatives (cyclopentenenes) range from 5.0-6.0 c.p.s. and in several bicyclo (2.2.2) octene derivatives (cyclohexenes) from 7.5-10.0 c.p.s.^{90a}, suggesting that here also a ring size effect is operative^{90b}.

The coupling between a bridgehead methine and an adjacent vinyl proton has similarly shown a dependence on ring size, being in the range of 2.4-3.0 c.p.s. for norbornene derivatives^{90a}, whereas in bicyclo (2.2.2) octenes and bicyclo (3.2.1) oct-2-enes these coupling constants lie in the range 6.1-7.1 c.p.s.^{90a,91,92}. The similarity between J_{AB} and J_{AX} in the keto olefin 66 and the J_{AB} and J_{AX} couplings of model bicyclooctene systems therefore provides good evidence for the presence of an identical unit in the olefin 66 but it does not in itself permit a distinction between a bicyclo (3.2.1) and bicyclo (2.2.2) octene system. It is noteworthy that, because of the rigidity of the bicyclo

octene rings, an allylic coupling between the hydrogens on C-6 and C-22 cannot occur by the normal σ - π mechanism. Presumably in these cases a σ bond mechanism is operative since the intervening C-H and C-C bonds exist in the geometrically favourable 'W' arrangement^{93,94,76}.

The carbonyl group of the keto olefin 66 was found to possess an enhanced $n \rightarrow \pi^*$ absorption ($\lambda_{\max} = 294 \text{ m}\mu$ ($\epsilon = 140$)) and a strongly positive Cotton effect curve with maxima at $316 \text{ m}\mu$ ($M = +27,200$) and $305 \text{ m}\mu$ ($M = +23,100$).

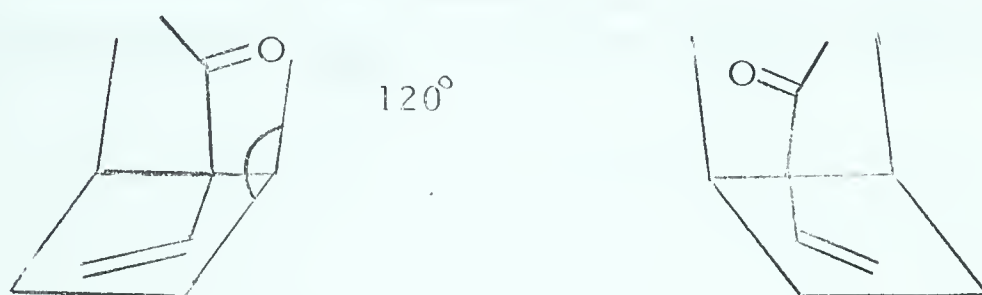
The characteristically high amplitude ultraviolet and rotatory dispersion curves of $\beta\gamma$ unsaturated ketones was first encountered in the sesquiterpenes, parasantonide (67a) and santonide (67b), and at that time a possible relationship between the spectral properties and some structural feature of the molecule was suggested⁹⁵.



67 a) $R = \text{CH}_3$; $R' = \text{H}$
b) $R = \text{H}$; $R' = \text{CH}_3$

This suggestion has since been supported by further investigations^{96,97,98}, which have shown that these optical properties come from mixing of the forbidden $n \rightarrow \pi^*$ transition with the allowed $\pi \rightarrow \pi^*$ transition in which an electron is transferred from the $\text{C}=\text{C}$ double bond to an antibonding orbital of the carbonyl group. Since this is only

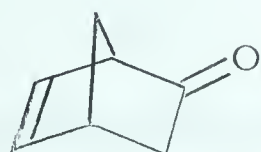
possible when the π orbital overlaps both the σ orbital and the π^* orbital of the carbonyl group, it follows that the enhanced absorption intensity will be observed only for certain orientations of the two functional groups. One such favored arrangement, which is found in both the santonides and in the keto olefin 66, is represented by the part structure A in which two planes defined by OC_1C_2 and $C_2C_3C_4$ intersect at a dihedral angle of about 120° .



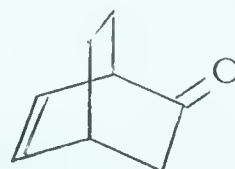
A

B

An important characteristic of this interaction is the marked sensitivity to small changes in a molecule near the chromophoric unit. For example, (+) bicyclo (2.2.1) hept-5-en-2-one (dehydronorcamphor (68)) possesses a positive Cotton effect curve with extrema at $322\text{ m}\mu$ ($[\text{M}] +46,400$), $311\text{ m}\mu$ ($[\text{M}] +30,800$) and $281\text{ m}\mu$ ($[\text{M}] -31,300$) whereas in (+) bicyclo (2.2.2) oct-5-en-2-one (69), the rotational values of the positive Cotton effect curve are considerably reduced in magnitude (extrema at $321\text{ m}\mu$ ($[\text{M}] +28,600$), $309\text{ m}\mu$ ($[\text{M}] +22,600$) and $290\text{ m}\mu$ ($[\text{M}] -13,800$))^{98,99}.



68



69

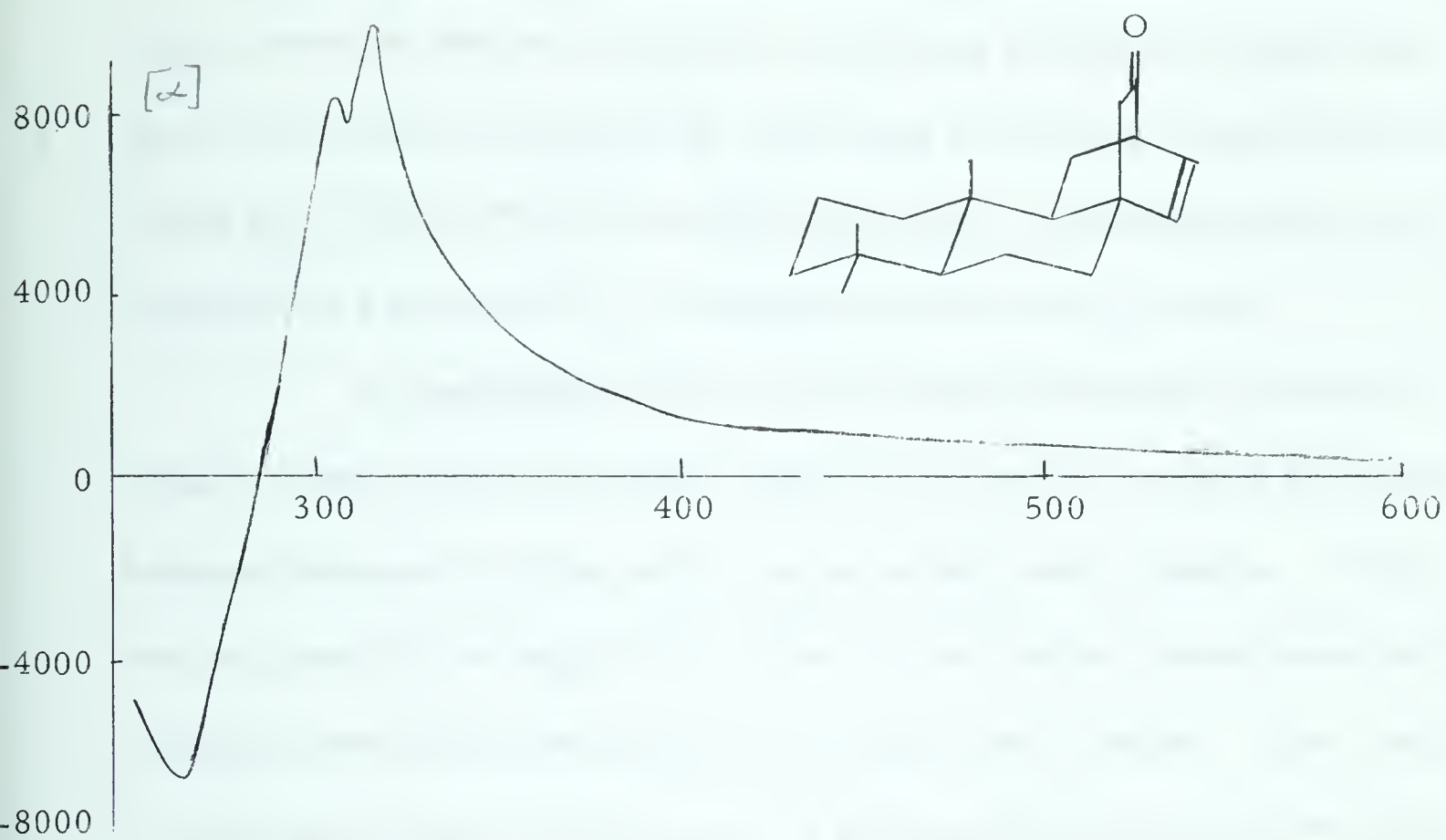


Figure 26. R.D. Curve of the β Unsaturated Ketone 66

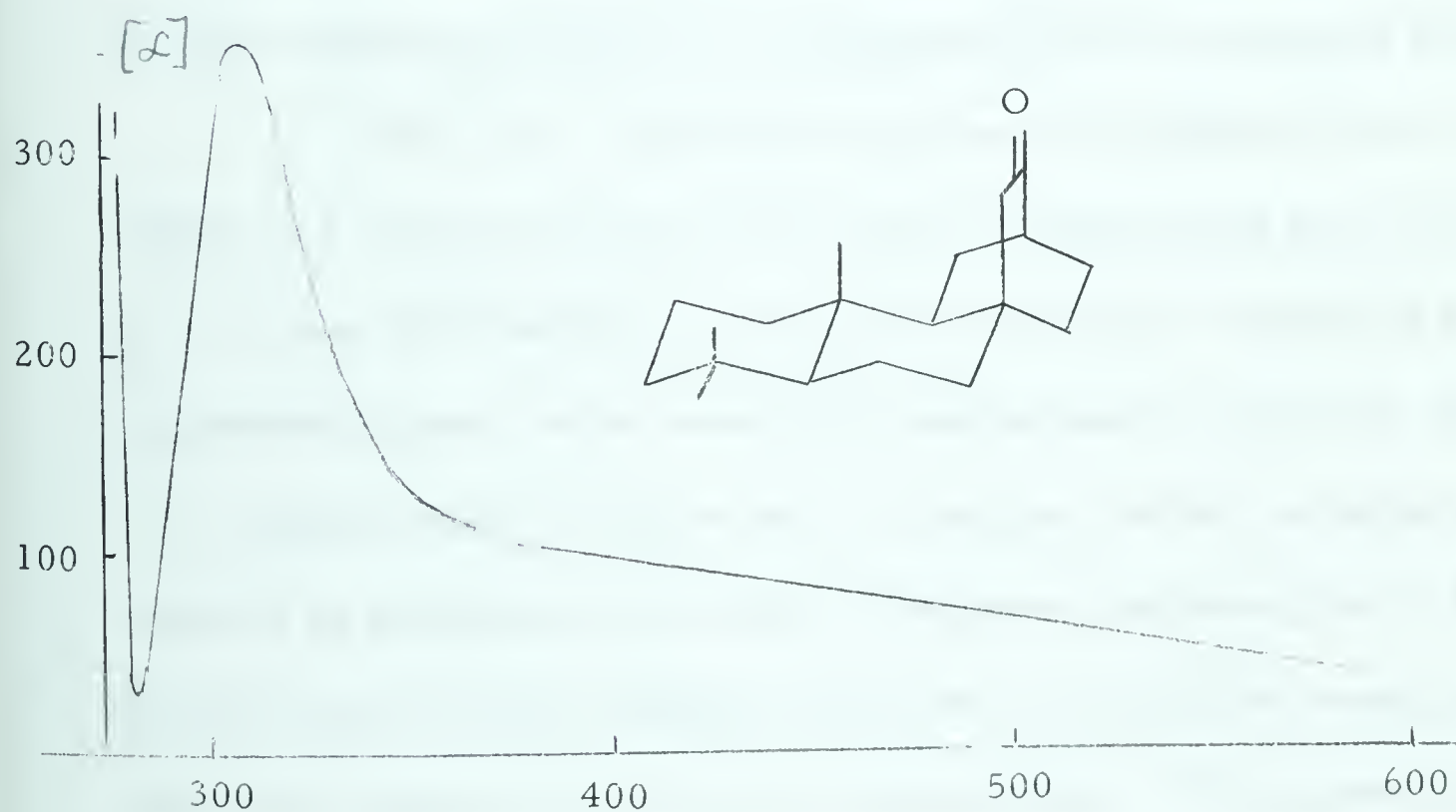


Figure 27. R.D. Curve of the Saturated Ketone 70

Although it was not possible to obtain the complete Cotton effect curve for the keto olefin 66, the strong similarity which it did show to the model compound 69 in the long wavelength region (extrema at $316\text{ m}\mu$ ($[\text{M}] +27,200$) and $309\text{ m}\mu$ ($[\text{M}] +23,100$)) supports the presence of a bicyclo (2.2.2) octenone system here as well.

An important aspect of the rotatory dispersion curve is related to the sign of the Cotton effect curve which, in the $\beta\gamma$ unsaturated ketones discussed to this point, has invariably been positive. There are two possible arrangements of the carbon-carbon double bond and the carbonyl group which will give rise to enhanced rotation. One, which is expressed by part structure A, is distinguished by a positive Cotton effect curve, the other, its enantiomer (structure B), is associated with a negative Cotton effect. The positive Cotton effect curve observed for the keto olefin 66 is therefore in agreement with the assigned structure.

The n.m.r. spectrum contained two signals in the C-methyl region, a 3 proton peak at 9.17τ and a six proton peak at 9.11τ . Since the C-16 and C-17 methyls in all previous examples containing the C-1 gem dimethyl group were invariably nonequivalent, it follows that the 9.17τ signal cannot be due to the C-12 angular methyl as might have been expected by comparison with other compounds containing the C-7 keto function (viz. the keto dimethyl esters 59, 60 and 65) but must instead represent either the C-16 or C-15 methyl group. This downfield shift of ca. 0.07 p.p.m. for the C-17 protons, which accompanies introduction of the C-21,22 double bond, can be attributed to a deshielding effect since

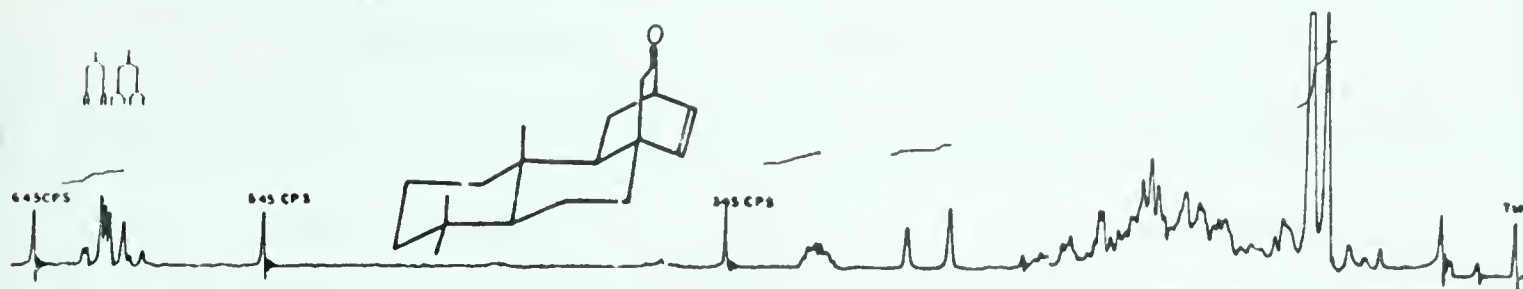


Figure 28. Nuclear magnetic resonance spectrum of the keto olefin 66.
at 100 mc.

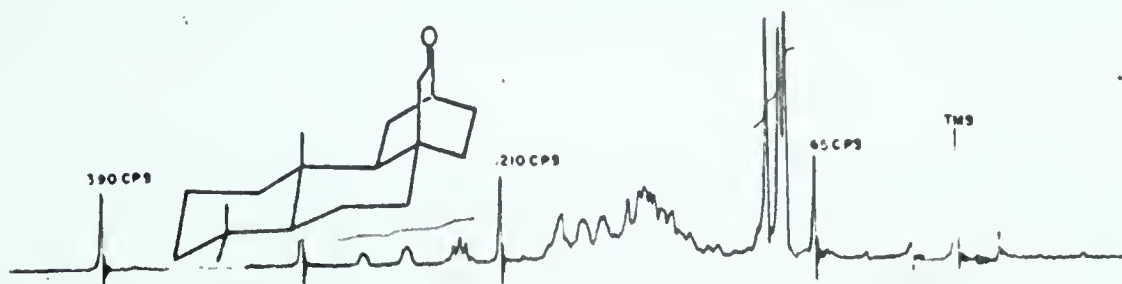
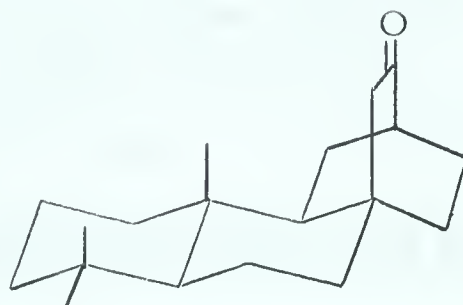


Figure 65. Nuclear magnetic resonance spectrum of the dihydroketone 67.
at 100 mc.

these protons lie in the plane of the olefinic group.

The mass spectrum obtained from the keto olefin 66 possessed a molecular ion at $m/e = 272$ in agreement with the assigned structure and, in addition showed a strong peak at $M-42$ (6.5% of total ionization) resulting from the elimination of ketene in a retro Diels-Alder reaction¹⁰⁰.

Hydrogenation of the keto olefin 66 at atmospheric pressure with 5% palladium-charcoal provided a quantitative yield of the dihydroketone 70, m.p. $126.5-27^\circ$, molecular ion at $m/e = 274$.

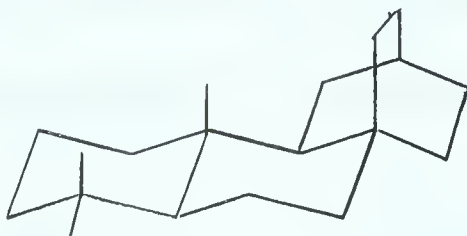


70

The keto group was identified by infrared absorption at 1717 cm^{-1} and by a positive Cotton effect curve (extrema at $312\text{ m}\mu[\alpha] + 360^\circ$ and $283\text{ m}\mu[\alpha] + 29^\circ$). The methylene group α to the carbonyl function (C-8) was again identified by an infrared band at 1404 cm^{-1} . The methyl groups appeared as three proton signals in the n.m.r. spectrum at 9.21 , 9.19 and 9.12τ . The low field peak can be assigned with confidence to either the C-15 or C-16 methyl on the basis of previously discussed compounds in the gem dimethyl series. An assignment of the two remaining signals, however, is difficult because both are equally well identified with either the C-12 angular methyl and the high field component of the C-1 gem dimethyl group. Thus, in five compounds of this series already discussed

this methyl group resonated between 9.17 and 9.20 τ while the angular methyl at C-12 in the 7 keto compounds (59, 60 and 65) was found at 9.16, 9.20 and 9.17 τ respectively.

The ketone 70 was reduced to the hydrocarbon 71, $m/e = 260$, $C_{19}H_{32}$, m.p. 86-86.5°C, in 80% yield by the Barton modification of the Wolff-Kishner reduction. The infrared spectrum of the hydrocarbon

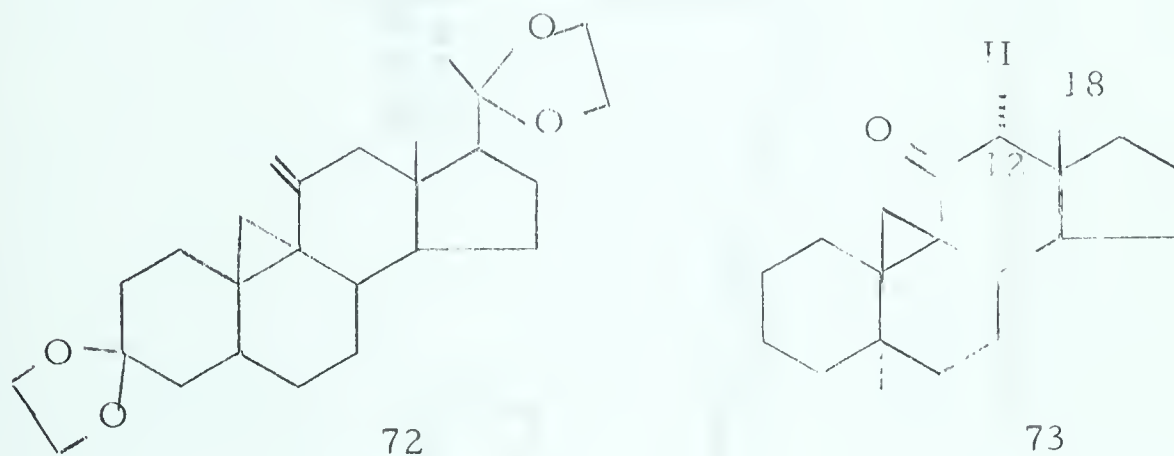


71

71 contained the expected broad absorption band between 2850 and 2950 cm^{-1} due to the C-H stretching vibration and a second strong absorption band at 1455 cm^{-1} presumably resulting from a combination of methylene scissoring and asymmetrical methyl bending vibrations. The symmetrical methyl vibrations were identified by a sharp, medium intensity band at 1385 cm^{-1} and a second peak at 1368 cm^{-1} due to the gem dimethyl group. The methylene rocking mode was characterized by a strong band at 728 cm^{-1} .

The n.m.r. spectrum contained three signals in the C-methyl region, located at 9.18, 9.15 and 9.05 τ . The low field peak, which was distinguished by a small coupling of 1.2 c.p.s., is assigned to the C-17 methyl group because of its virtual identity with the chemical shift value of the angular methyl in saturated maleopimaric acid derivatives (viz. 9.05, 9.05, 9.05 and 9.06 τ in compounds 43b, 43c, 44b and 51 respectively).

No attempt has been made to identify the proton involved in the long range coupling with the methyl group although one of the α protons at C-11, C-4 or C-13 is probably involved since they are all capable of providing the geometrically favorable 'W' arrangement necessary for the transmission of spin information through the small lobe of the sigma bonds^{76,93,94}. This suggestion is supported by the identification of a similar long range coupling with the C-18 methyl group in two related steroid derivatives 72¹⁰¹ and 73¹⁰², which in the latter case was shown to involve the C-12 axial proton.



The enantiomeric hydrocarbon 76 was prepared in these laboratories by G. G. Iverach from a sample of the hemiacetal 74 kindly supplied by Dr. O. E. Edwards of the National Research Council, Ottawa. The hemiacetal was converted to the aldehyde 75 by the published procedure (Wolff-Kishner reduction followed by chromium trioxide oxidation¹⁴⁵) and the aldehyde reduced to the hydrocarbon 76, m.p. 84-85°, m/e = 260 by a modification of the procedure employed by Vorbruggen and Djerassi²⁰ for a similar reduction in the veatchine series.

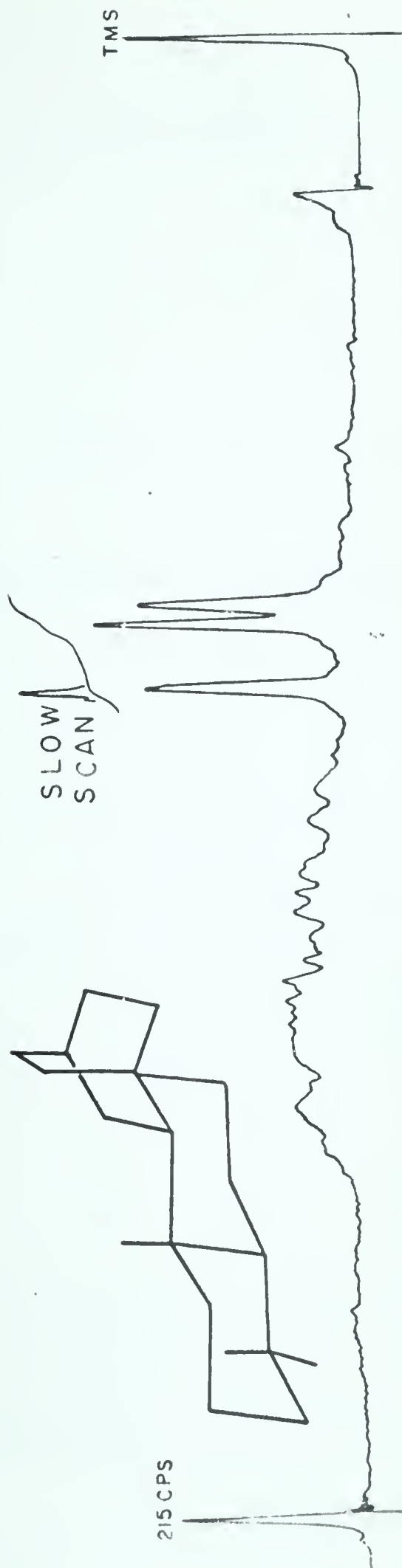


Figure 29. Nuclear magnetic resonance spectrum of the hydrocarbon 71. at 100 mc.



Figure 30. Infrared spectrum of the hydrocarbon 71.

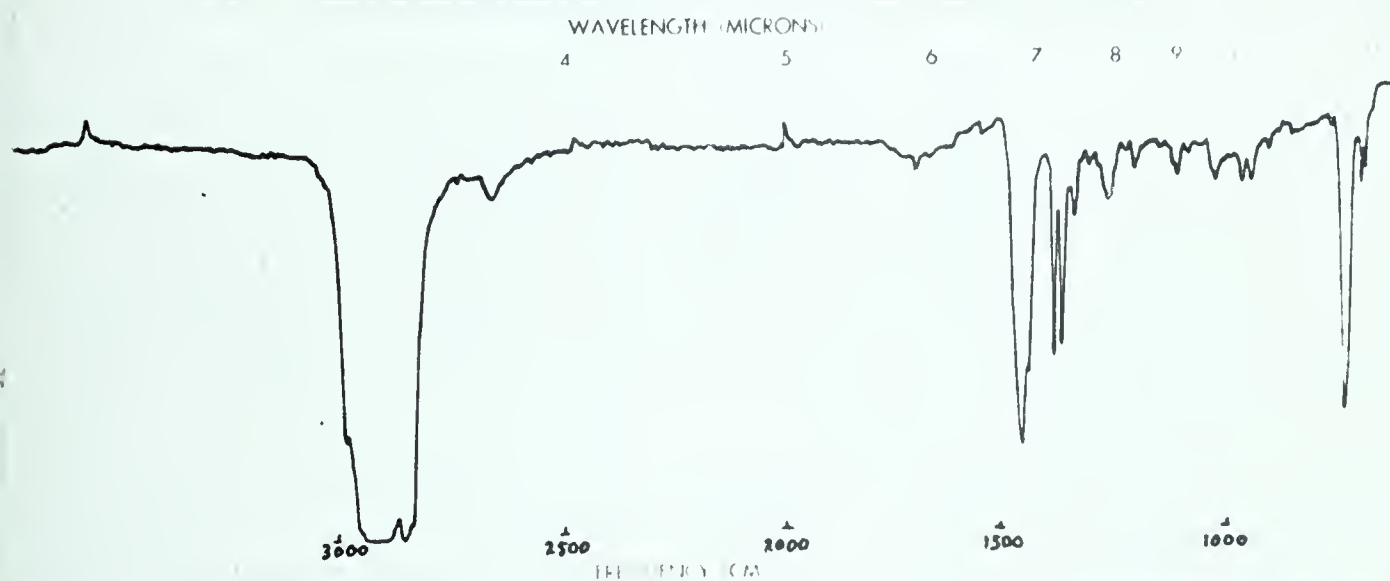
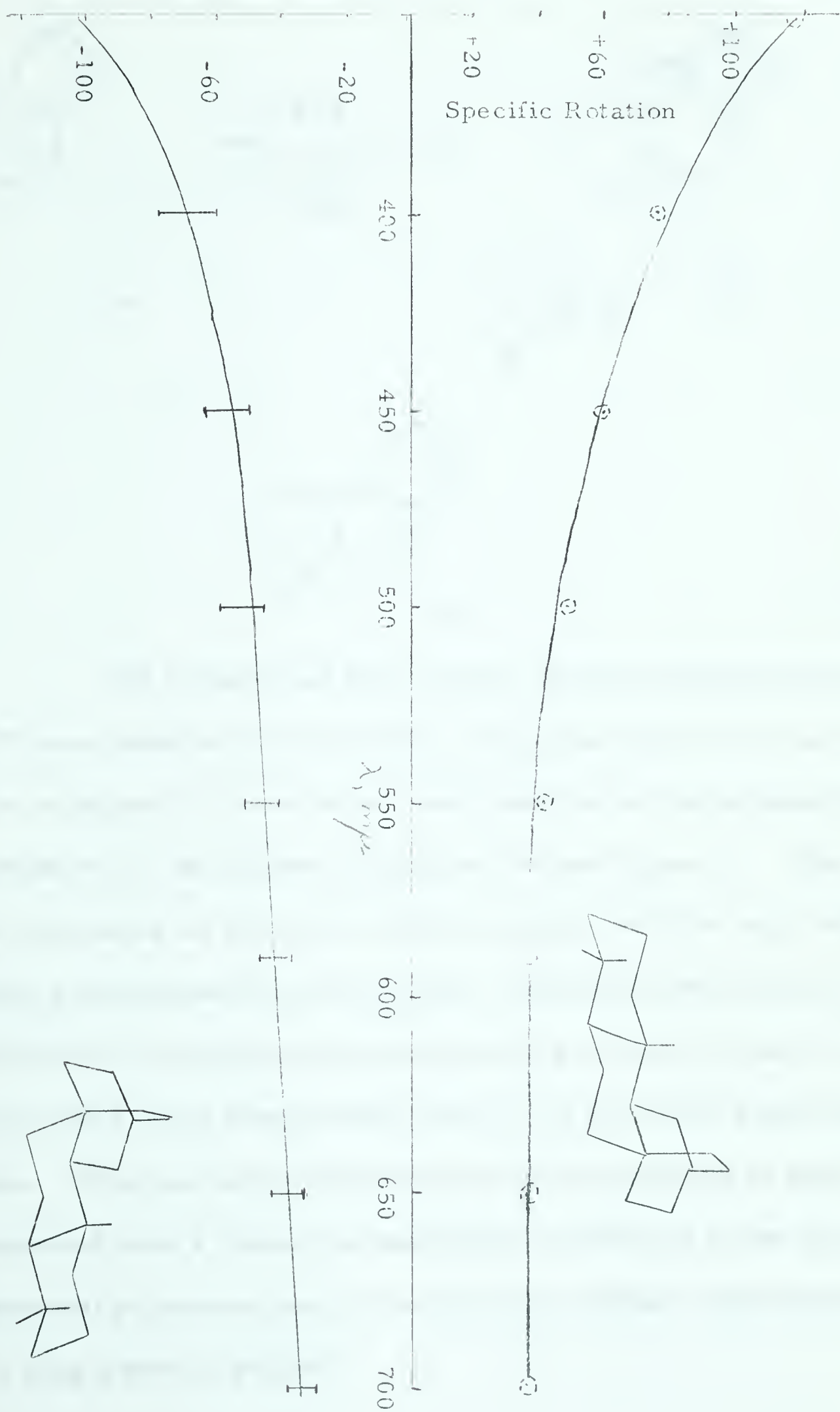
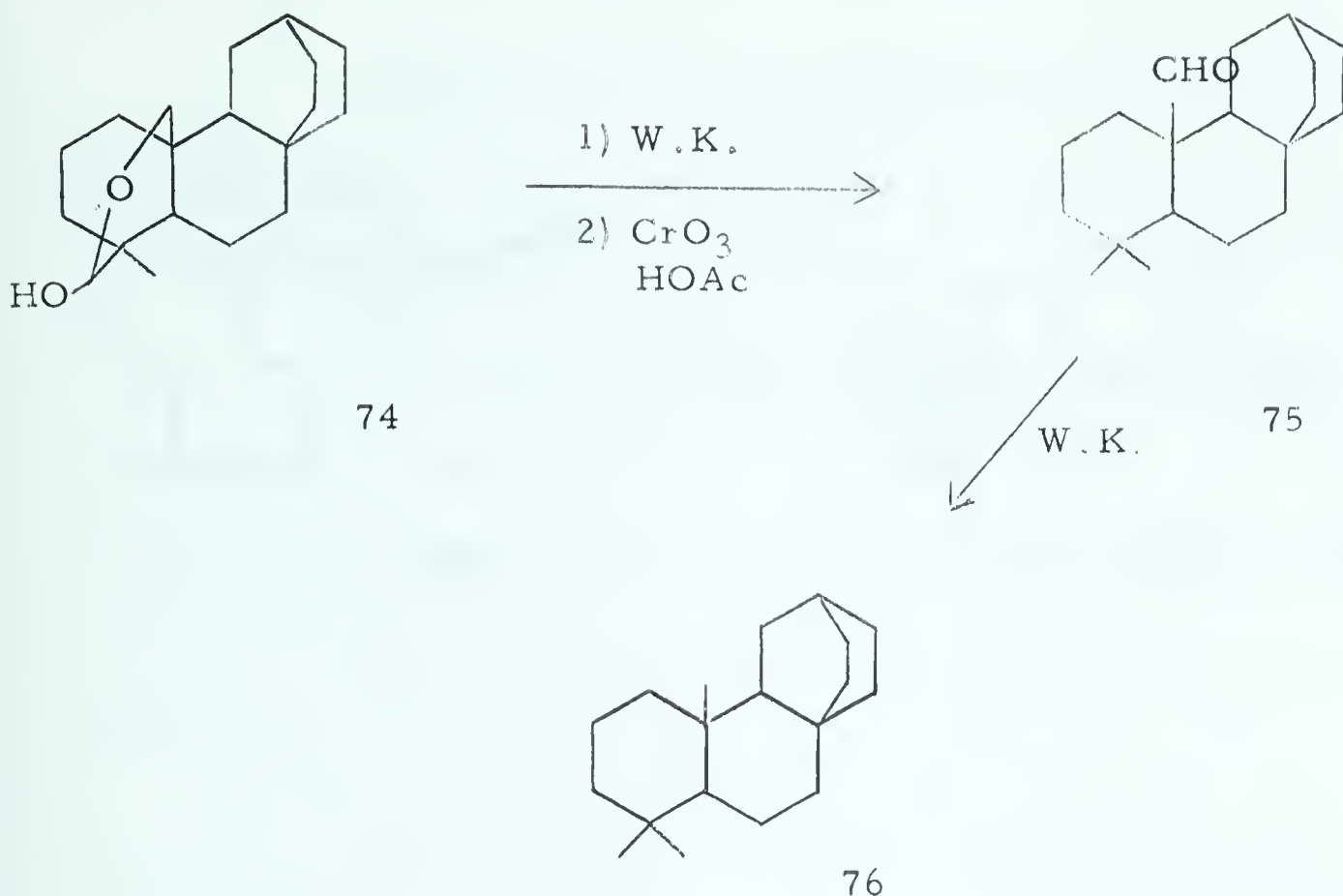
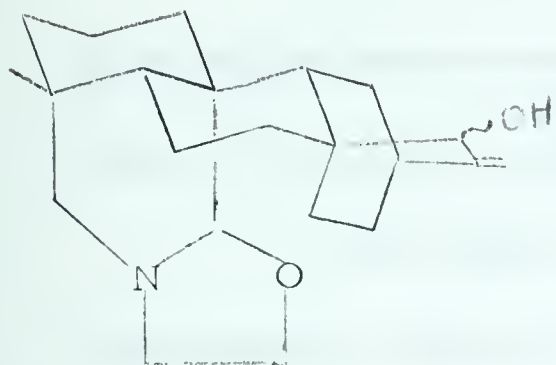


Figure 31. Infrared spectrum of the atisine hydrocarbon 76.

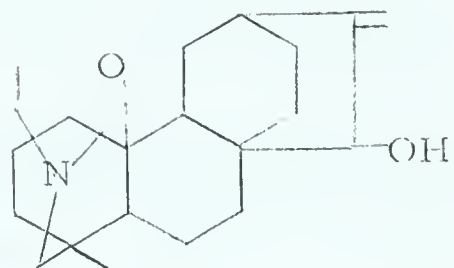




The infrared and mass spectra of the two hydrocarbons 71 and 76 were identical but the rotatory dispersion curves bore an enantiomeric relationship to each other, being positive for the hydrocarbon 71 and negative for the atisine hydrocarbon 76 (see Figure I). This correlation represents the first interrelation of atisine with the resin acids through a tetracycyclic intermediate, confirming the mirror image relationship of the perhydrophenanthrene ring system in these two series and providing direct experimental proof of the trans-anti backbone in atisine. This conclusion therefore permits the structure of atisine to be expanded from a planar representation (structure 4) to the three dimensional representation (11) in which the complete stereochemistry of the ring system is defined.



(11)



4

C. EXPERIMENTAL

Infrared spectra were measured on Perkin Elmer Recording Infrared Spectrometers, Models 21 and 421, using sealed sodium chloride cells. The solvent, unless otherwise noted was carbon tetrachloride.

For routine ultraviolet absorption spectra a Cary Recording Spectrometer, Model 14 M was employed. Spectra of the far ultraviolet region were measured with a Unicam SP 700 Spectrometer equipped with a nitrogen purging system. The solvent, unless otherwise stated, was 95% ethanol.

Nuclear magnetic resonance spectra unless otherwise stated were measured in ca. 20% w/v solution of chloroform or deuterio-chloroform using a Varian Associates Model A-60, HR-60 or HR-100 spectrometer with tetramethylsilane as an internal standard.

Melting points were determined either on a hot stage or on a Herschberg melting point apparatus using a set of Anschutz thermometers. The thermometers in both cases were calibrated against N.B.S. melting point standards. The melting points reported are corrected values.

Optical rotatory dispersion spectra were measured on a Rudolph Automatic Recording Spectropolarimeter.

For gas chromatography a Perkin Elmer Model 154D Vapor Fractometer was used.

Skellysolve B refers to Skelly Oil Company light petroleum, b.p. 62-70°C.

Microanalyses are by Pascher Mikroanalytisches Laboratorium, Bonn, West Germany, and C. Daessle, Montreal, Quebec.

I. FORMATION OF MALEOPIMARIC ACID (28a).

a) From abietic acid (27a).

Abietic acid was purified by the procedure described in Organic Synthesis, vol. 32, p. 1. Ultraviolet spectrum: $\lambda_{\max}$ 241 m μ (ϵ = 13,920); reported: $\lambda_{\max}$ 241 m μ (ϵ = 14,130). Infrared spectrum: $\bigvee_{\max}^{\text{CHCl}_3}$ 1694 (s), 1630 cm⁻¹ (w).

Abietic acid (13.4 g., 44.4 mmoles) was heated in a sealed tube with maleic anhydride (5 g., 51 mmoles) according to the procedure of Ruzicka et. al.³¹ (8 hours/160°C). The crude product was washed with water to remove unreacted maleic anhydride and recrystallized from glacial acetic acid. The yield of maleopimaric acid was 5.7 g. (32%). The analytical sample, m.p. 227-8°C (reported³¹ 227-8°C) was prepared by recrystallization from glacial acetic acid. Calc. for C₂₄H₃₂O₅ (28a): C, 71.99; H, 8.06%. Found: C, 71.76; H, 8.03%. Infrared spectrum: $\bigvee_{\max}^{\text{CHCl}_3}$ 1849 (m), 1788 (s), 1702 (s), 1643 cm⁻¹ (w).

b) From commercial rosin (colophonium; Fisher Scientific Co.).

The rosin used in these experiments possessed the following spectral properties. Infrared spectrum: $\bigvee_{\max}^{\text{CHCl}_3}$ 1695 cm⁻¹ (s). Ultraviolet spectrum: 224 m μ (ϵ = 8,400), 236 m μ (ϵ = 8,900), 242 m μ (ϵ = 8,700). Nuclear magnetic resonance spectrum (CCl₄): τ = 9.18 (3H, assigned), 9.00 (6H, J = 7 c.p.s.), 8.75 (3H), 4.73 (1H, broad)

4.33 ($\sim 1H$), 3.0-3.3 (~ 0.5).

The integrated absorption values for the aromatic and olefinic regions indicated contamination by ca. 17% of aromatic material, probably dehydroabietic acid.

Reaction of the rosin with excess maleic anhydride in refluxing p-cymene solution for 4 hours under nitrogen provided maleopimaric acid in 34% yield. Maleopimaric acid was also obtained from Eastman Organic Chemicals, Eastman Kodak Co..

The methyl ester of maleopimaric acid (28b), methyl maleopimarate, was most conveniently prepared on a small scale by reaction with ethereal diazomethane. Recrystallization from benzene provided the purified sample, melting point 214-15 C (reported³¹ 214-15 C).

Infrared spectrum: $\bigvee_{\text{max}}^{\text{CHCl}_3}$ 1849 (m), 1782 (s), 1722 (s), 1643 cm^{-1} (w).

Nuclear magnetic resonance spectrum: $\tau = 9.41$ (3H), 9.00 (6H; $J = 6.9$ c.p.s.), 8.84 (3H), 6.33 (3H), 4.45 (1H).

For large scale preparations of methyl maleopimarate (28b) it was found more convenient to employ the following procedure.

Maleopimaric acid (140 g., 0.35 moles) was dissolved in benzene and refluxed gently for three hours with 100 g. of thionyl chloride. The solution was then concentrated and the precipitated acid chloride (31) collected on a filter and washed with anhydrous ether. The crude product (120 g., 80% yield) gave a positive Beilstein test and showed carbonyl absorption at $\bigvee_{\text{max}}^{\text{CHCl}_3}$ 1850 (m) and 1780 cm^{-1} (s).

The acid chloride (22 g., 0.053 moles) was dissolved in 75 mls.

of pyridine (Karl Fisher reagent, dried over KOH), 35 mls. of anhydrous methanol added, and the solution stirred at room temperature for 10 hours. The pyridine was then removed at the steam bath under reduced pressure, benzene added, and the solution dried over anhydrous magnesium sulfate, filtered and concentrated. The crude methyl maleopimarate (28b), m.p. 206-11°C (19 g., 83% yield) crystallized from the solution on dilution with pentane. Recrystallization from benzene-pentane raised the melting point to 214-17°C. The infrared spectrum was identical with that of the sample prepared from maleopimaric acid by esterification with ethereal diazomethane.

c) Attempted Diels-Alder addition of vinyl acetate to abietic acid.

Abietic acid (10 g.) was dissolved in xylene, vinyl acetate (14 g.) added, and the mixture heated in a sealed tube at 185°C for 40 hours. Unreacted vinyl acetate (13.7 g., 98% recovery) was collected by vacuum distillation and the xylene solvent removed by a subsequent steam distillation. The residue was then taken up in ether and extracted with aqueous sodium hydroxide. Acidification of the basic extracts with aqueous HCl yielded 6.6 g. (66% recovery) of crystalline abietic acid identified by infrared spectral comparison with authentic material.

The ether solution was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The resulting oil showed strong carbonyl bands at $\nu_{\max}$ 1805 and 1740 cm^{-1} but was clear of further carbonyl absorption. The infrared spectrum was very similar to that of the dimeric anhydride of abietic acid ($\nu_{\max}$ 1802 and

1738 cm^{-1}) prepared from the acid chloride ($\nu_{\text{max}}\ 1775\text{ cm}^{-1}$) according to the procedure of Vogel (Practical Organic Chemistry. Longmans, Green and Co., p. 367).

II.

a) Conversion of maleopimaric acid (28a) to fumaropimaric acid (32a).

Maleopimaric acid (10 g., 25 mmoles) was refluxed in 200 mls. of aqueous methanol (1:10) containing potassium hydroxide (16 g.) for 1.5 hours. The solution was then concentrated under reduced pressure and acidified with dilute hydrochloric acid. The white precipitate was filtered, washed with water and recrystallized trice from acetic acid to give 4 g. of fumaropimaric acid, m.p. $193-95^{\circ}\text{C}$. Repeated recrystallization from aqueous ethanol and then acetic acid, followed by drying under vacuum at 110°C for several days provided the analytical sample, m.p. $193-95^{\circ}\text{C}$ (reported $249-52^{\circ}\text{C}^{54}$, (from dioxane), 225°C , $280-82^{\circ}\text{C}$ (methanol- CHCl_3)). Calc. for $\text{C}_{24}\text{H}_{34}\text{O}_6 \cdot \text{H}_2\text{O}$ (32a): C, 66.03; H, 8.31; O, 25.65%. Found: C, 66.14; H, 8.05; O, 25.90%.

Fumaropimaric acid could also be recrystallized from ethyl acetate (m.p. $187-92^{\circ}\text{C}$) and aqueous ethanol (m.p. $244-48^{\circ}\text{C}$). The infrared spectra of the fumaropimaric acid preparations recrystallized from ethyl acetate and acetic acid were similar to each other but distinctly different from the sample obtained by recrystallization from aqueous ethanol. Fumaropimaric acid could also be converted to a higher melting modification, m.p. $228-38^{\circ}\text{C}$ on heating under vacuum at 180°C for

5 hours. Subsequent recrystallization from acetic acid restored the melting point to 193-95°C.

b) Conversion of fumaropimaric acid (32a) to maleopimaric acid (28a).

Fumaropimaric acid (0.215 g.) was sublimed at 245°C onto a cold finger over a period of two hours. Three recrystallizations of the sublimed material from acetic acid provided maleopimaric acid, m.p. 226-28°C identified by infrared spectral comparison with authentic material (nujol mull).

In an unsuccessful attempt to effect this conversion 0.230 g. of fumaropimaric acid was dissolved in 20 mls. of acetic anhydride and the solvent slowly distilled off at atmospheric pressure. The final traces of acetic anhydride were removed by dissolving the oily residue in ether and washing several times with water. The ether solution was then dried over anhydrous magnesium sulfate, filtered and evaporated. The oily mixed anhydride possessed infrared absorption at 1825 and 1750 cm^{-1} but was clear of carbonyl absorption at ca. 1710 cm^{-1} .

The mixed anhydride was reconverted to fumaropimaric acid by refluxing it for 70 minutes in 8 mls. of aqueous ethanol (3:1 volume ratio) containing 12 drops of concentrated hydrochloric acid. The crystalline residue obtained on evaporation of the solvent was washed with water and recrystallized once from acetic acid. The infrared spectrum was identical with that of fumaropimaric acid.

c) Establishment of configuration at C-21 of fumaropimaric acid.

i) Retro Diels-Alder reaction of the trimethyl ester 32b.

Esterification of fumaropimaric acid with ethereal diazomethane provided the corresponding oily trimethyl ester 32b. Infrared spectrum: $\nu_{\max}$ 1730 (s), 1645 cm^{-1} (w). Nuclear magnetic resonance spectrum: $\tau=9.42$ (3H), 8.93 (3H, $J=6$ c.p.s.), 8.89 (3H), 6.38 (3H), 6.31 (3H), 6.27 (3H), 4.66 (1H). R.D. in methanol ($C=0.382$): plain positive dispersion curve; $[\alpha]_D +19^\circ$, $[\alpha]_{500} +34^\circ$, $[\alpha]_{400} +77^\circ$, $[\alpha]_{350} +130^\circ$, $[\alpha]_{300} +273^\circ$, $[\alpha]_{260} +420^\circ$.

A sample of the trimethyl ester 32b was placed in a glass tube and distilled under vacuum at 270°C . The crystalline material which condensed on the cold portion of the tube was resublimed at 150°C yielding colorless plates, m.p. $103-104.5^\circ\text{C}$, $\nu_{\max}$ 1730 (s), 1645 cm^{-1} (m). The infrared spectrum and melting point were identical with those of authentic dimethyl fumarate. The mixture melting point was undepressed. The oily residue left from the initial distillation possessed ultraviolet absorption at $265\text{ m}\mu$.

ii) Retro Diels-Alder reaction of the cis trimethyl ester 34.

The trimethyl ester 34 (1.18 g.) was placed in a vacuum distillation apparatus and heated under vacuum at 300°C with a sand bath. The oily distillate possessed a refractive index, $n_D^{19.9} = 1.453$ which compared favorably with the value of $n_D^{19.9} = 1.442$ reported for dimethyl maleate. The infrared spectrum was also very similar to that of dimethyl maleate but contained several additional bands between 1000 and 1100 cm^{-1} attributed to the presence of some starting material. The undistilled residue again exhibited an ultraviolet maximum at $265\text{ m}\mu$.

d) Evidence for the intermediacy of a methyl ester in the conversion of maleopimaric acid to fumaropimaric acid.

Maleopimaric acid (5.0 g., 12.5 mmoles) was refluxed in methanol (75 mls.) for 15 minutes, 4N aqueous potassium hydroxide (25 mls.) added and refluxing continued for two hours. The solution was then concentrated under reduced pressure and diluted with 225 mls. of 5% aqueous hydrochloric acid. The white precipitate was collected on a filter, washed with water, dried under vacuum at 150-60°C for 1.5 hours, esterified with ethereal diazomethane and chromatographed on 140 g. of neutral alumina. Elution with benzene (2.0 l.) provided 1.52 g. (30% yield) of the oily triester 32b identified by means of its infrared spectrum. Elution with ether-benzene (1:50, 0.4 l. and 1:25, 0.5 l.) resulted in no further recovery of material. Elution with 10% ether in benzene (0.5 l.) yielded 10 mgs. of the crystalline cis triester 34 identified by its infrared spectrum. The crystalline saturated lactone dimethyl ester 43c was similarly isolated in trace amounts on elution with 0.7 l. of 25% ether in benzene, identification again being made by means of infrared spectral comparison. Finally, elution with 5% acetic acid in ether (2.0 l.) provided 1.4 g. (30% recovery) of methyl maleopimarate (28b) identified by means of melting point, mixture melting point and infrared spectral comparison with authentic material.

In the control experiment 5.0 g. (12.5 mmoles) of maleopimaric acid (28a) was dissolved in 25 mls. of 4N aqueous potassium hydroxide and heated on the steam bath for 12 minutes, methanol (75 mls.)

was then added and refluxing continued a further two hours. The subsequent isolation procedure was identical with that of the main experiment. Elution with benzene (0.7 l.), 2% ether-benzene (0.5 l.) and 4% ether-benzene (0.5 l.) did not yield any trans trimethyl ester (32b). As before, elution with 10% ether in benzene (0.5 l.) and 25% ether in benzene (0.5 l.) provided trace amounts of crystalline cis trimethyl ester 34 (11 mgs.) and saturated lactone dimethyl ester 43 c (7 mgs.), identified by means of infrared spectral comparisons. Finally, elution with 2.5 l. of 5% acetic acid in ether provided 2.3 g. (45% recovery) of methyl maleopimarate, identified by melting point, mixture melting point and infrared spectral comparison.

e) Hydrolysis of maleopimaric acid under non-epimerizing conditions.

(i) Maleopimaric acid (5.0 g., 12.5 mmoles) was dissolved in 100 mls. of 8% aqueous potassium hydroxide, heated on the steam bath for 12 minutes, then cooled and acidified with 50% aqueous hydrochloric acid. The precipitate was collected by filtration, dried for 18 hours at room temperature and atmospheric pressure, esterified with ethereal diazomethane and chromatographed on 160 g. of acid washed alumina (activity 3). Elution with benzene (1.2 l.), 6% ether in benzene (0.7 l.) and 25% ether in benzene (0.5 l.) gave 1.55 g. (27% yield) of the cis trimethyl ester 34, m.p. 102-04°C, infrared spectrum identical with that of authentic material. Elution with ether (0.5 l.) and 5% acetic acid in ether (2.0 l.) provided 1.6 g. (31% recovery) of methyl maleopimarate identified by means of its infrared spectrum.

In a control experiment, 2.5 g. (6.0 mmoles) of maleopimaric acid was processed as above, except that prior to esterification with ethereal diazomethane the crude product was heated under vacuum at 155°C for two hours in order to complete the anhydride ring closure. Chromatography on 85 g. of acid washed alumina (activity 3) gave only the anhydride 28b identified by its infrared spectrum.

(ii) Maleopimaric acid was dissolved in pyridine and water added until incipient turbidity. The solution was heated on a steam bath for 6 hours and then concentrated by distillation under reduced pressure. The crystalline precipitate obtained by filtration showed extensive melting at 140-50°C, solidifying and remelting at 227°C.

f) Attempted decarboxylation of fumaropimaric acid (32) with lead tetraacetate.

Fumaropimaric acid (0.27 g.) was suspended in 400 mls. of acetonitrile containing 0.5 mls. of pyridine and stirred for 16 hours at 50° with 0.286 g. (0.645 mmoles) of lead tetraacetate. Ethylene glycol was then added and stirring continued 30 minutes to destroy unreacted lead tetraacetate, the solution concentrated, water added and the organic material taken up in chloroform. The oily product obtained by evaporation of the chloroform could not be satisfactorily crystallized from aqueous methanol or benzene-pentane solution. Esterification and chromatography did not provide any identifiable products.

g) Preparation of the C-1 hydroxymethyl derivatives of maleopimaric acid.

- (i) Reduction of the acid chloride 31 to the hydroxy anhydride 35 with sodium borohydride.

The acid chloride 31 (23 g., 0.057 moles) was dissolved in 250 mls. of diglyme (distilled from LiAlH_4). Sodium borohydride (1.3 g., 0.039 moles) in diglyme (50 mls.) was added dropwise at room temperature with rapid stirring over a period of 45 minutes and stirring continued an additional 3 hours. Dilute aqueous HCl (50 mls.) was then added and after 30 minutes, the organic product was precipitated by the addition of a large volume of water and extracted with ether. The ether solution was extracted with 5% aqueous sodium hydroxide, washed with water, dried over anhydrous magnesium sulfate and evaporated to give 1.9 g. (9% yield) of the crude hydroxy anhydride 35 which crystallized on standing. Recrystallization from benzene-Skellysolve B provided the analytical sample, m.p. 151-53 C. Calc. for $\text{C}_{24}\text{H}_{34}\text{O}_4$: C, 74.56; H, 8.87; O, 16.56%. Found: C, 74.36; H, 9.00; O, 17.03%. Infra-red spectra: $\bigvee_{\text{max}}^{\text{CHCl}_3}$ 3630 (w), 3480 (w), 1848 (m), 1782 cm^{-1} (s). Nuclear magnetic resonance spectrum: $\tau=9.39$ (3H), 9.24 (3H), 9.00 (6H; $J=7$ c.p.s.), 4.46 (1H).

- (ii) Conversion to the dimethyl ester 36.

The hydroxy anhydride (1.4 g., 0.0036 moles) was refluxed in 50 mls. of methanol for 60 minutes, the solution cooled and treated with ethereal diazomethane until a permanent yellow color was developed. The methanolic solution was then concentrated and the resulting oil dissolved in ether and passed through a short column of acid washed

alumina. The crude dimethyl ester 36 (~ 1.4 g.) crystallized on evaporation of the ether eluent. The analytical sample, m.p. $148-50^{\circ}\text{C}$, was prepared by recrystallization from ethyl acetate and then methanol-water. Calc. for $\text{C}_{26}\text{H}_{40}\text{O}_5$: C, 72.19; H, 9.32; O, 18.49%. Found: C, 72.14; H, 9.40; O, 18.50%. Infrared spectrum: ν_{max} 3640 (m), 1745 cm^{-1} (s). Nuclear magnetic resonance spectrum: $\tau=9.35$ (3H), 9.24 (3H), 8.94 (3H, $J=7$ c.p.s.), 8.90 (3H, $J=7$ c.p.s.), $7.08-7.22$ (3H), 6.72 (1H, $J=10$ c.p.s.), 6.43 (6H), 4.55 (1H).

h) Reduction of the acid chloride 31c to the hydroxy lactone 37.

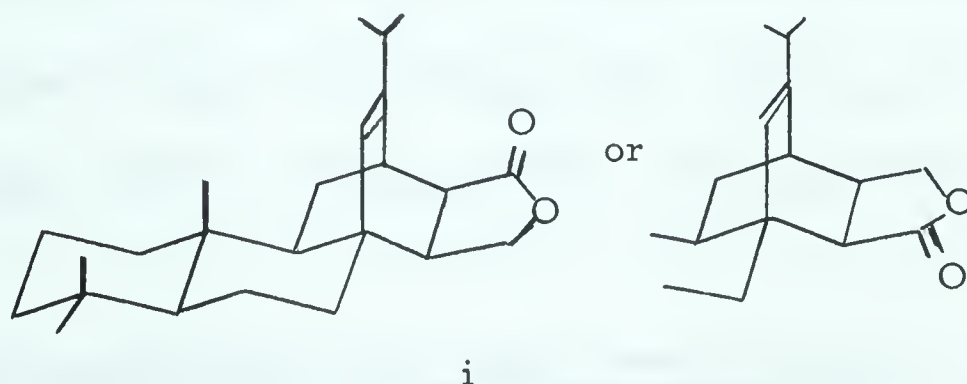
The acid chloride 31 (4 g., 9.2 mmoles) was added to a solution of sodium borohydride (0.50 g., 13.5 mmoles) in diglyme (15 mls.) and stirred at $85-90^{\circ}\text{C}$ for two hours. Dilute hydrochloric acid was then added and the solution concentrated on the steam bath by sweeping out the diglyme and water with a stream of nitrogen. The residue was taken up in chloroform, washed several times with water and evaporated. Recrystallization from ether provided the analytically pure hydroxy lactone 37, m.p. $172-76^{\circ}\text{C}$. Calc. for $\text{C}_{24}\text{H}_{36}\text{O}_3$: C, 77.38; H, 9.74; O, 12.88%. Found: C, 77.56; H, 9.63; O, 13.37%. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3610 (w), 3475 (w), 1759 cm^{-1} (s). Nuclear magnetic resonance spectrum: $\tau=9.38$ (3H), 9.24 (3H), 9.00 ($J=7$ c.p.s.), 8.95 (6H, $J=7$ c.p.s.), 8.08 (1H), 7.40 (1H), 6.73 (1H, $J=11$ c.p.s.), 4.43 (1H).

j) Reduction of maleopimaric acid with sodium borohydride.

Preparation of the lactone i.

Maleopimaric acid (15 g., 0.0374 moles) was dissolved in

diglyme and added slowly to a solution of 1.5 g. (0.045 moles) of sodium borohydride in diglyme at 85°C. The solution was stirred at this temperature for two hours, then acidified with dilute hydrochloric acid and concentrated at the steam bath. The residue was dissolved in chloroform, washed several times with water, dried over anhydrous magnesium sulfate and recrystallized from ether and ethyl acetate. The analytical sample of the lactone acid i, melted at 214-20°C. Calc. for $C_{24}H_{34}O_4$: C, 74.56; H, 8.86; O, 16.56%. Found: C, 74.61; H, 8.69; O, 16.57%. Infrared spectrum: $\nu_{\max}$ 1758 (s), 1700 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.37 (3H), 8.94 (6H, $J=6.5$ c.p.s.), 8.81 (3H), 7.25-7.75 (~ 3 H), 5.84 (1H, $J=9$ c.p.s.), 4.42 (1H).



k) Preparation of the *cis* trimethyl ester 34.

Small scale conversion of maleopimaric acid to the triester 34 were most readily achieved by esterifying a methanolic solution of maleopimaric acid with ethereal diazomethane and removing unreacted anhydride by passing the crude product through a short column of alumina.

When larger quantities of the trimethyl ester were required, the following procedure employing the acid chloride 31 was found to be more convenient.

620 g. (1.5 moles) of the acid chloride 31 was refluxed for 10 hours in 2.5 l. of anhydrous methanol and the solution then concentrated at the steam bath under reduced pressure until precipitation of the trimethyl ester commenced. Evaporation was then discontinued and the solution allowed to stand at room temperature. Filtration provided 450 g. (65% yield) of the trimethyl ester 34, m.p. 98-101°C. The analytical sample, m.p. 103-5°C (reported⁴⁹, 103°C) was prepared by recrystallization from methanol. Calc. for $C_{27}H_{40}O_6$: C, 70.39; H, 8.75; O, 20.84; OCH_3 , 20.20%. Found: C, 70.32; H, 8.79; O, 21.02; OCH_3 , 20.18%. Infrared spectrum $\nu_{\max}$ 1749 (sh), 1730 (s), 1648 cm^{-1} (w). Nuclear magnetic resonance spectrum: $\tau=9.38$ (3H), 8.95 (3H, $J=7.1$ c.p.s.), 8.91 (3H, $J=7.1$ c.p.s.), 8.85 (3H), 6.47 (6H), 6.33 (3H), 4.67 (1H). R.D. in methanol ($C=0.294$) plain positive dispersion curve $[\alpha]_D$ 0°, $[\alpha]_{450}$ 0°, $[\alpha]_{400} + 8^\circ$, $[\alpha]_{350} + 35^\circ$, $[\alpha]_{325} + 65^\circ$, $[\alpha]_{300} + 135^\circ$, $[\alpha]_{275} + 316^\circ$, $[\alpha]_{260} + 620^\circ$.

1) Partial saponification of the *cis* trimethyl ester 34.

Preparation of the mono acid 41.

The trimethyl ester 34 (1.00 g., 2.18 mmoles) was dissolved in 53 mls. of methanol, 34 mls. of water containing 0.2 g. (5 mmoles) of sodium hydroxide added, and the solution refluxed 5 hours. Aqueous HCl was then added, the solution concentrated and the white precipitate collected

by filtration and washed with water. Recrystallization from methanol and benzene-pentane provided the analytical sample of the monoacid 41, melting point 183-85°C. Calc. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58; O, 21.50; OCH_3 , 13.90%. Found: C, 69.61; H, 8.54; O, 21.63; OCH_3 , 13.89%. Infrared spectrum: $\nu_{\max}$ 3400-2500 (broad), 1730 (s), 1705 (s), 1652 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ =9.40 (3H), 8.91 (6H, $J=7.5$ c.p.s.), 8.85 (3H), 7.0-7.8 (4H, complex), 6.37 (3H), 6.30 (3H), 4.59 (1H).

The monoacid 41 (0.235 g.), m.p. 180-84°C was heated under vacuum in a sublimation block at 290°C for 20 minutes. Resublimation of the product at 80°C provided a small amount of monomethyl fumarate, m.p. 143-45°C (reported 144.5°C). The infrared spectrum (nujol mull) was identical with that of authentic material.

Esterification of the monoacid 41 with diazomethane provided the oily trans trimethyl 32b, identified by its infrared spectrum.

m) Preparation of methyl fumaropimarate 42.

(i) From methyl maleopimarate (28b).

Methyl maleopimarate (60 g., 0.145 moles) was refluxed in 600 mls. of 1.5 molar methanolic sodium hydroxide for 45 minutes, 400 mls. of 2 molar aqueous sodium hydroxide added and refluxing continued a further 100 minutes. The solution was then neutralized with aqueous hydrochloric acid, concentrated and acidified. The white precipitate which separated was collected by filtration and washed, first with water and then with benzene. Two recrystallizations from acetic acid

provided 15 g. (24% yield) of the diacid 42, m.p. 269-79°C. The analytical sample, m.p. 274-79°C, was prepared by further recrystallization from 95% ethanol. Calc. for $C_{25}H_{36}O_6$: C, 69.40; H, 8.39; O, 22.20; OCH_3 , 5.69%. Found: C, 69.49; H, 8.35; O, 22.10; OCH_3 , 4.98%. Infrared spectrum: $\checkmark_{\text{max}}^{\text{nujol}}$ 3200 (broad), 1725 (s), 1705 cm^{-1} (s).

(ii) Saponification of the cis trimethyl ester 34.

The cis trimethyl ester (105 g., 0.228 moles) was dissolved in 700 mls. of methanol, 950 mls. of aqueous 2 molar sodium hydroxide added and the solution refluxed for 90 minutes. The pH was then adjusted to 7, the solution concentrated and finally acidified. The impure diacid 42, m.p. 264-74°C, was collected by filtration, washed with water and dried (wt. 40 g., 40% yield). Two recrystallizations from 95% ethanol provided 29 g. of the purified sample, m.p. 274-79°C.

(iii) Preparation of methyl fumaropimarate from the Diels-Alder addition of fumaric acid to methyl abietate (27b).

Preparation of methyl abietate.

Rosin (N.F., Fisher Scientific Co.) (1780 g., 5.9 moles) was dissolved in 2.5 liters of methanol containing 360 g. (6.4 moles) of potassium hydroxide, the solution cooled to 15°C with an ice-bath and 500 mls. of dimethyl sulfate added. After the initial reaction had subsided (an ice-water bath was applied at this point to control the temperature of the solution) an additional 500 g. of dimethyl sulfate was added and the solution allowed to stand overnight at room temperature. The reaction mixture was then poured into a six litre separatory funnel con-

taining 4 litres of water, shaken, and the lower organic layer dissolved in ca. 1.5 l. of ether. The ether solution was washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The yield of methyl abietate, obtained as a dark viscous oil, was 1720 g. (92% conversion). Infrared spectrum: $\nu_{\max}$ 3075 (w), 1720 cm^{-1} (s). Nuclear magnetic resonance spectrum (CCl_4): $\tau=9.20$, 9.0 ($J=6$ c.p.s.), 8.81, 6.38 (3H), 4.72 and 4.32 ($\sim 1\text{H}$), 3.24 and 3.00 ($\sim 1\text{H}$). Integration of the aromatic and olefinic regions indicated that the preparation of methyl abietate was contaminated by ca. 30% aromatic material, presumably methyl dehydroabietate.

Methyl abietate was also obtained commercially from Eastman Organic Chemicals, Distillation Products Industries.

Diels-Alder Addition.

Crude methyl abietate (830 g., 2.6 moles), prepared from the dimethyl sulfate esterification of rosin, was stirred with 500 g. (4.4 moles) of fumaric acid at 170-85°C for 18 hours under a nitrogen blanket. The product was then transferred to a 2-litre Erlenmeyer flask, allowed to cool, and washed portionwise with 2 litres of benzene. The benzene insoluble residue was suspended successively in 3, 2 and 1 litre of hot water, the insoluble portion being collected each time by filtration. In this manner 202 g. (18% yield) of the pure diacid 42 was obtained and identified by melting point, mixture melting point and infrared spectral comparison with the sample prepared by saponification of the cis trimethyl ester 34. The yield, after adjusting for the presence of methyl dehydro-

abietate in the starting material, was 26%.

n) Epimerization of the *cis* trimethyl ester with potassium methoxide.

Potassium metal (1.0 g., 0.026 moles) was dissolved in 40 mls. of anhydrous methanol, 0.511 g. (0.0011 moles) of the trimethyl ester 34 added, the solution stoppered under a nitrogen blanket and allowed to stand for $3\frac{1}{2}$ days at room temperature. The solvent was then evaporated, water added and the reaction product extracted with ether. The ether solution was washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The oily residue (0.22 g., 43% yield) was shown to be the trans trimethyl ester 32b by comparison of its infrared spectrum with that of an authentic sample.

o) Acid catalyzed hydrolysis of the *cis* trimethyl ester 34.

A solution of 0.550 g. (1.20 mmoles) of the trimethyl ester 34 in 25 mls. of acetic acid containing 10 drops of conc. sulfuric acid was heated for 20 hours on the steam bath, then diluted with water and the organic precipitate taken up in ether. The ether solution was dried over anhydrous magnesium sulfate, filtered and evaporated. Three recrystallizations of the solid product (0.370 g., 75% yield) from acetic acid provided methyl maleopimarate (28b) m.p. 218-20°C, identified by mixture melting point and infrared comparison with authentic material.

In another experiment the *cis* trimethyl ester 34 (0.317 g.) was dissolved in 1.5 mls of redistilled BF_3 etherate and allowed to stand at room temperature for two hours. Water was then added, the

organic product extracted three times with benzene, the combined extracts washed several times with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. One recrystallization from benzene-Skellysolve B provided 30 mgs. of methyl maleopimarate, melting point 215-217°C after a second recrystallization. The identity was confirmed by mixture melting point and infrared spectral comparison with an authentic sample.

p) Partial saponification of the saturated lactone dimethyl ester 43c.

(i) Preparation of starting material.

The following adaptation of the method reported by Brus and coworkers³⁸ was employed for large scale preparations of the saturated lactone diacid 43a.

Maleopimaric acid (175 g., 0.437 moles) was dissolved in 4 litres of 0.5 molar sodium hydroxide, the solution acidified to pH 6.5 and stirred overnight. During this period some precipitation of maleopimaric acid occurred (infrared identification) and was presumably responsible for neutralizing the solution (pH 7.0). The anhydride was redissolved with aqueous sodium hydroxide, the solution diluted to ca. 8 litres and reacidified with aqueous HCl to pH 6.5. The use of dilute solutions seemed necessary to avoid precipitation of starting material. Stirring was then continued for 3 days, after which the crude lactone acid 43a, m.p. 248-63°C, was precipitated by the addition of aqueous HCl, collected by filtration, washed and recrystallized from aqueous ethanol. The yield of purified lactone acid, melting point 272-73°C was 155 g. (82%).

Calc. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; O, 22.94%. Found: C, 68.18; H, 8.04; O, 23.51%. Infrared spectrum: $\nu_{\max}^{\text{nujol}}$ 3500-2500 (broad), 1756 (s), 1740 (sh), 1711 cm^{-1} (s). $\nu_{\max}^{\text{CH}_3\text{CN}}$ 1774 (s), 1738 cm^{-1} (s).

Esterification with diazomethane provided the corresponding dimethyl ester 43c, melting point 218-20°C, after recrystallization from benzene-pentane. Calc. for $C_{26}H_{38}O_6$: C, 69.97; H, 8.58; O, 21.50%. Found: C, 69.91; H, 8.68; O, 21.35%. Infrared spectrum: $\nu_{\max}$ 1780 (s), 1745 (s), 1730 cm^{-1} (s); $\nu_{\max}^{\text{CHCl}_3}$ 1770 (s), 1738 (s), 1730 cm^{-1} (s); $\nu_{\max}^{\text{CH}_3\text{CN}}$ 1772 (s), 1733 cm^{-1} (s). Nuclear magnetic resonance spectrum: $\tau=9.05$ (3H), 9.03 (6H, $J=6.5$ c.p.s.), 8.85 (3H), 6.35 (6H).

(ii) Partial saponification of the lactone dimethyl ester 43c.

The saturated lactone dimethyl ester (62 g., 0.148 moles) was refluxed for 5.5 hours in 500 mls. of aqueous dioxane (1:2) containing 6.4 g. (0.16 moles) of sodium hydroxide. The solution was then acidified with aqueous HCl, concentrated at the steam bath under reduced pressure and the crude lactone monoacid 43c, melting point 228-33°C, collected by filtration. The yield, after one recrystallization from methanol, was 57 g. (84%; corrected for 1 molecule of solvated methanol). The analytical sample was prepared by recrystallization from benzene-pentane and methanol. Calc. for $C_{25}H_{36}O_6$: C, 69.40; H, 8.39; O, 22.20; OCH_3 , 7.17%. Found: C, 69.43; H, 8.41; O, 22.19; OCH_3 , 7.18%. The percentage weight loss on predrying for 3 hours at 110°C was 6.25. Calc. for 1 molecule of solvated methanol, 6.90%. Infrared spectrum: $\nu_{\max}^{\text{CHCl}_3}$ 3400-2400 (broad), 1767 (s), 1723 (s), 1717 cm^{-1} (sh). Nuclear magnetic

resonance spectrum: τ 9.05 (3H), 9.0 (6H, $J=6.5$ c.p.s.), 8.85 (3H), 6.33 (3H).

The lactone monoacid 43b was reconverted to starting material with ethereal diazomethane, identified by melting point, mixture melting point and infrared spectral comparison.

q) Saponification of the saturated lactone diacid 43a.

15.0 g. (0.036 moles) of the saturated lactone diacid 43a was refluxed in 335 mls. of 1.14 molar aqueous sodium hydroxide for 4 days, then acidified with 100 mls. of 50% aqueous HCl, the precipitate collected by filtration washed with water and dried overnight at room temperature. The crude product was then dissolved in 100 mls. of dioxane and the insoluble silicic acid removed by filtration. Evaporation of the dioxane filtrate yielded an oil which was heated under vacuum for 1.5 hours at 150°C. Infrared spectral analysis indicated an increase in the amount of anhydride in the crude product following this heating process. Benzene was then added and the impure hydroxy acid 44a (4.1 g., 26% yield) removed by filtration, washed several more times with benzene and recrystallized from aqueous-ethanol to provide the analytical sample, m.p. 250-52°C. Calc. for $C_{24}H_{36}O_7$: C, 66.03; H, 8.32; O, 25.65%. Found: C, 65.82; H, 8.48; O, 26.06%. Infrared spectrum: $\nu_{\text{max}}^{\text{nujol}}$ 3419 (m), 2400-3350 (broad), 1732 (s), 1697 (s), 1667 cm^{-1} (s).

A sample of the hydroxy acid 44a was dissolved in methanol and converted to the corresponding trimethyl ester 44b with ethereal diazomethane. Recrystallization from methanol provided the analytical

sample, melting point 176-78°C. Calc. for $C_{27}H_{42}O_7$: C, 67.76; H, 8.84; O, 23.41; OCH_3 , 19.45%. Found: C, 67.61; H, 8.88; O, 23.45; OCH_3 , 19.75%. Infrared spectrum: $\nu_{\max}$ 3470 (broad), 1728 (s), 1710 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.05 (3H), 8.94 (6H, $J=7$ c.p.s.), 8.83 (3H), 7.60 (1H), 7.1 (1H, $J=4$ c.p.s.), 6.7 (1H, t., spacing 4 c.p.s.), 6.33 (6H), 6.27 (3H), 5.73 (1H, hydroxyl).

Dilution studies on the hydroxy trimethyl ester did not alter the nature of the infrared absorption in the hydroxyl region.

The benzene soluble portion of the hydrolysis product (12 g.) was esterified with diazomethane and chromatographed on 800 g. of silica gel. A benzene forerun (1.2 l.) gave no recovery of material. Elution with 5% ether in benzene provided, in the first three fractions, 0.5 g. of impure trans trimethyl ester 32b. Fractions 5-11 (0.6 l.) contained 5.2 g. of methyl maleopimarate, melting point 215-17°C, after recrystallization from benzene-pentane, the identification confirmed by mixture melting point and infrared spectral comparison. Fractions 12-18 (0.6 l.) yielded impure hydroxy trimethyl ester 44b (1.6 g.) and fractions 27-38 (elution with 1.2 l. of 1:10 and 1:4 ether-benzene) 1.2 g. of impure lactone dimethyl ester 43b.

The fractions rich in 32b, 43b and 44b were all contaminated by varying amounts of anhydride, presumably methyl maleopimarate, which was removed in each case by filtration through a short column of alumina. The infrared spectrum of the purified olefin was identical with that of the trans trimethyl ester 32b. The n.m.r. spectrum, however,

contained an additional peak at 9.20 τ (isopropyliden ϵ) in addition to signals at τ 9.40, 8.87, 6.41, 6.33, 6.30 and 4.63 characteristic of the trimethyl ester 32b. The ratio of exo-endo olefin was estimated to be ca. 1:2. Final purification of the hydroxy trimethyl ester 44b by recrystallization from methanol provided a sample, m.p. 176-79°C, infrared spectrum superimposable upon that of authentic material. Similarly, recrystallization of the saturated lactone dimethyl ester 43b from benzene-pentane provided the purified sample, m.p. 218-20°C confirmed by mixture melting point and infrared spectral comparison.

r) Studies on the hydroxy triacid 44a and the trimethyl ester 44b.

(i) A sample of the analytically pure hydroxy acid was heated under vacuum at 175°C for 4 hours. The infrared spectrum (nujol mull) was identical with that of starting material. No anhydride formation was detected.

(ii) The hydroxy triacid (0.065 g., 0.15 mmoles) was dissolved in 10 mls. of pyridine containing 0.075 g. (0.364 mmoles) of N,N' dicyclohexylcarbodiimide, the solution heated on the steam bath for 4 hours and then evaporated. The residual oil showed no infrared absorption between 1750 and 1800 cm^{-1} .

(iii) A solution of 0.390 g. (0.82 mmoles) of the hydroxy trimethyl ester was heated 4 hours on the steam bath in 16 mls. of anhydrous pyridine containing 5.4 mls. of phosphorous oxychloride. Chloroform was then added and the solution washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. Filtration

of the residue through a short column of alumina (15 g., elution with ether) yielded a colorless oil consisting of 1 major and 2 minor components by t.l.c. analysis (alumina, KMnO_4 spray). Calc. for the isopropylidene trimethyl ester $45 \text{ C}_{27}\text{H}_{40}\text{O}_6$; C, 70.39; H, 8.75; O, 20.84%. Found: C, 69.84; H, 8.13%. Nuclear magnetic resonance spectrum: τ 9.19, 8.86, 8.45, 7.78 (2H), 6.8-7.5 ($\sim 3\text{H}$), 6.32, 6.30, 6.27.

A small peak in the n.m.r. spectrum at $\tau=9.39$ indicated the presence of ca. 20% trans trimethyl ester 32b.

(iv) 0.050 g. of the isopropylidene trimethyl ester was sealed under nitrogen in a glass tube and partially inserted in a sublimation block at 250°C . After 20 hours the tube was removed and the sublimate collected (wt. 5 mgs., 33% yield). The infrared spectrum and melting point ($101-103^\circ\text{C}$) showed it to be dimethyl fumarate.

s) Decarboxylation of maleopimaric acid with $\text{Pb}(\text{OAc})_4$ in pyridine.

Maleopimaric acid (5.0 g., 0.0125 moles) was reacted with lead tetraacetate (8.3 g., 0.019 moles) in pyridine (75 mls.) at 50°C . After 1 hour excess reagent was destroyed with ethylene glycol and the pyridine solvent removed at the steam bath under reduced pressure. Water was then added and the organic material taken up in three ether washes. These were combined, washed several times with a saturated salt solution, dried over anhydrous magnesium sulfate, filtered and evaporated to give 4.3 g. of an oily residue which was chromatographed on 300 g. of silica gel.

Elution with benzene (1.0 l.) provided 1.82 g. (32% yield) of

the oily olefin mixture 46, vacuum distilled at 220°C to provide the analytical sample. Calc. for $C_{23}H_{30}O_3$: C, 77.91; H, 8.53; O, 13.54%. Found: C, 77.31; H, 8.84; O, 14.00%. Infrared spectrum: $\nu_{\max}$ 3080 (w), 3030 (w), 1855 (m), 1775 (s), 1636 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ 9.55, 9.48, 9.27, 9.00 ($J=7$ c.p.s.), 8.38, 5.52, 5.28, 4.77, 4.40.

The olefin mixture gave a strong positive test with tetra nitro-methane.

Elution with benzene-ether (5:1; 0.6 l.) provided 0.74 g. (14% yield) of the acetoxy anhydride 48. Recrystallization from benzene-Skellysolve B and ethyl acetate provided the analytical sample, m.p. 181-83°C. Calc. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27; O, 19.31; OAc, 10.34%. Found: C, 72.33; H, 8.13, O, 19.37; OAc, 11.96%. Infrared spectrum $\nu_{\max}^{CHCl_3}$ 1845 (m), 1785 (s), 1725 (s), 1630 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ 9.43 (3H), 9.00 (6H, $J=7$ c.p.s.), 8.60 (3H), 8.04 (3H), 4.45 (1H).

Esterification of the olefin mixture 46, with methanolic diazo-methane followed by filtration through a short column of neutral alumina provided the exo methylene dimethyl ester 47, melting point 121-23°C after recrystallization from methanol. Calc. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06; O, 15.97%. Found: C, 75.57; H, 9.23; O, 15.06%. Infrared spectrum $\nu_{\max}$ 3078 (w), 1750 (s), 1642 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ 9.51 (3H), 8.97 (3H, $J=7$ c.p.s.), 8.91 (3H, $J=7$ c.p.s.), 7.14 (2H), 6.45 (6H), 5.53 (1H), 5.28 (1H), 4.55 (1H).

t) Attempted decarboxylation of methyl maleopimarate (28b).

(i) Methyl maleopimarate (4.4 g., 0.011 moles) was dissolved in pyridine (75 mls.) containing lead tetraacetate (7.4 g., 0.017 moles) and the solution stirred for six hours at 50°C. During this time the solution slowly turned from a dark brown to a deep red color although gas evolution was not detected. Ethylene glycol was then added, the solvent removed at the steam bath under reduced pressure, and water added. The organic precipitate was extracted with ether, dried over anhydrous magnesium sulfate, filtered and evaporated. The recovery of methyl maleopimarate, identified by melting point and infrared spectral comparison, was 86%.

In another experiment 3.3 g. (0.008 moles) of methyl maleopimarate was dissolved in 60 mls. of pyridine at 97°C. The addition of 5.4 g. (0.012 moles) of lead tetraacetate was followed by an immediate evolution of gas and a rise in the solution temperature to 104°C. After 12 hours, ethylene glycol was added and the reaction processed as before. The recovery of methyl maleopimarate, identified by its infrared spectrum was 82%.

(ii) Decomposition of lead tetraacetate with pyridine.

The addition of a sample of lead tetraacetate to 60 mls. of pyridine at 100°C resulted in the almost instantaneous evolution of gas and an increase in the solution temperature to 110°C.

A solution of lead tetraacetate in pyridine at 70°C was somewhat more stable, requiring an induction period of ca. 10 minutes before

gas evolution could be detected.

u) Decarboxylation of phenylacetic acid with lead tetraacetate.

Phenylacetic acid (10 g., 0.074 moles) was dissolved in 100 mls. of pyridine at room temperature and lead tetraacetate added at 15 minute intervals in four 12 g. aliquots (0.11 mole). Gas evolution reached a maximum shortly after addition of the second portion of $\text{Pb}(\text{OAc})_4$ and was accompanied by a rise in the reaction temperature to 45°C . The solution was kept at this temperature for the remainder of the reaction period (2.5 hours) after which the solvent was distilled off under reduced pressure through a Vigreux column. The dark residue was then dissolved in ether and the solution washed successively with distilled water, dilute HCl , saturated sodium bicarbonate solution and finally again with water. Following this, the ether solution was dried over anhydrous magnesium sulfate, filtered and evaporated to give 3.2 g. of oily residue which was subjected to chromatography on 125 g. of neutral alumina.

Elution with pentane (0.30 l.) provided 0.70 g. (4% yield) of bibenzyl, melting point $52-53^\circ\text{C}$ after recrystallization from 95% ethanol (reported for bibenzyl 52.5°C). The identity was further confirmed by mixture melting point and infrared spectral comparison with authentic material.

Elution with 25% ether in benzene (0.90 l.) provided 0.50 g. of a yellow oil, a portion of which was vacuum distilled at 120°C and subjected to G.L.C. analysis.

TABLE XII G.L.C. DATA 'O' COLUMN*

	Retention times	
Temperature: 174°C	Benzyl acetate	benzene-ether fraction
Detector Voltage: 8 v	1) 195 sec.(1 μ l.)	1) 92 sec., 195 sec., .3, μ l.
Carrier Gas: He	2) 194 sec.(1 μ l.)	2) 92 sec., 195 sec.,
Inlet pressure: 22 p.s.i.		
Flow meter: 6.6 cm		

TABLE XIII G.L.C. DATA "R" COLUMN†

	Retention times	
Temperature: 174°C	Benzyl aceate	benzene-ether fraction
Detector Voltage: 8 v	1) 821 sec. (1 μ l)	1) 329 sec., 814 sec., 891 (3 μ l.)
Carrier Gas: He	2) 822 sec. (1 μ l)	2) 329 sec., 817 sec., (3 μ l.)
Inlet pressure 25 p.s.i.	Methyl acetate	
Flowmeter 6 cm.	1) 881 sec.	
	2) 878 sec.	

* "O" Column silicone grease

† "R" Column ucon oil

The infrared spectrum of the benzene-ether fraction ($\nu_{\max}$ 3085 (w), 3065 (w), 3030 (m), 1740 cm^{-1} (s)) was similar to, but not identical with that of authentic benzyl acetate.

v) Attempted decarboxylation of the lactone acid 43b with $\text{Pb}(\text{OAc})_4$ /pyridine.

The lactone monoacid (3.5 g., 0.0081 moles) contaminated with ca. 5% of the dimethyl ester 43c, was reacted with 6.6 g. (0.015 moles) of lead tetraacetate in 50 mls. of pyridine at 30°C for 18 hours. Ethylene glycol was then added and the solution concentrated to a small volume. The organic material was taken up in ether (150 mls.), washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. Chromatography of the oily residue (3.1 g.) on 100 g. of neutral alumina provided ca. 7% yield of the dimethyl ester 43c on elution with 0.5 l. of 1:1 benzene-ether and 0.3 l. of ether (identification by melting point (215-16 C) and infrared spectrum). Elution with 0.1 l of chloroform yielded 0.85 g. of an oil ($\nu_{\max}$ 3620 (w), 3480 (broad), 1772 (s), 1723 (s) and 1640 cm^{-1} (s)) which could not be induced to crystallize. Additional intractable oils were obtained on continued elution with chloroform and chloroform-methanol (4:1).

w) Attempted decarboxylation of the monoacid 41 with $\text{Pb}(\text{OAc})_4$ /pyridine.

The monoacid (10 g. 0.0224 moles) was stirred at 30°C with 12 g. (0.027 moles) of lead tetraacetate in 100 mls. of pyridine. After 20 minutes a mild exothermic reaction set in, causing the temperature to rise to 35°C. After 40 minutes, 5.0 g. (0.011 moles) of lead tetraacetate was added and stirring continued for 60 minutes. Excess reagent was then destroyed with ethylene glycol, the solvent evaporated and chloroform added to the residue. The chloroform solution was extracted with 5% aqueous sodium hydroxide, washed with distilled water, evaporated, and the oily residue (4.0 g.) chromatographed on 150 g. of

acid washed alumina. Elution with 4% ether in benzene provided ca. 0.65 g. of colorless oil which after distillation under high vacuum at 185°C possessed the following spectral characteristics. Infrared spectrum: $\nu_{\max}$ 1730 (sh), 1720 (s), 1610 cm^{-1} (w). Nuclear magnetic resonance spectrum (CCl_4): τ 9.40 (~ 0.6 H), 9.25 (2.4 H), 8.94, 8.87, 8.00 (2.2 H), 6.43 and 6.36 (6 H), 4.81 (1 H). Ultra-violet spectrum: $\lambda_{\max}$ 237 $\text{m}\mu$.

III. REMOVAL OF THE ISOPROPYL GROUP IN MALEOPIMARIC ACID.

a) Preparation of the lactone dimethyl ester 50b.

Maleopimaric acid (15 g., 1.25 mmoles), dried under vacuum at 100°C to remove solvated acetic acid, was dissolved in 225 mls. of water containing 5 g. of sodium hydroxide (pH 8). Potassium permanganate (8.4 g.) in 225 mls. of water was added and the solution allowed to stand at 10°C for 8 hours. The reaction mixture was then acidified to pH 2 with aqueous HCl and the white precipitate collected and dried under vacuum at 100°C (wt. 14.4 g., 90% yield; m.p. 187-95°C). Recrystallization from ethyl acetate - acetone followed by drying under vacuum provided the purified lactone 50a as microneedles, m.p. 208-11°C (reported 212°C). Infrared spectrum: $\nu_{\max}^{\text{nujol}}$ 1780 (s), 1747 (s), 1714 cm^{-1} (s); $\nu_{\max}^{\text{CH}_3\text{CN}}$ 1772 (s), 1745 (sh), 1730 cm^{-1} (s).

Esterification with diazomethane and recrystallization from methanol provided the corresponding dimethyl ester 50b, melting point

183.5-85.5 C (reported 182-84 C). Calc. for $C_{26}H_{36}O_6$: C, 70.25; H, 8.18%. Found: C, 70.16; H, 8.08%. Infrared spectrum: $\checkmark_{\text{max}}^{CHCl_3}$ 1778 (s), 1745 (sh), 1728 (s), 1684 cm^{-1} (w); $\checkmark_{\text{max}}^{CH_3CN}$ 1770 (s), 1736 (sh), 1722 (s), 1675 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ 9.26 (3H), 8.84 (3H), 8.20 (6H), 6.35 (6H), 4.98 (1H). R.D. in methanol ($C_D = 0.280$) plain negative dispersion curve. $[\alpha]_D^{25} -47$, $[\alpha]_{500} -67$, $[\alpha]_{400} -146$, $[\alpha]_{350} -233$, $[\alpha]_{300} -488$, $[\alpha]_{280} -710$.

The dimethyl ester gave a positive test with tetranitromethane.

Earlier experiments which did not include pre-drying the maleopimaric acid gave erratic results. The yields of unsaturated lactone 50a were lower and in some cases it could not be isolated at all. One such experiment, which resulted in the isolation of the saturated lactone diacid 43a (as the dimethyl ester 43c) together with a poorly characterized hydroxy ester is described below.

Maleopimaric acid (5 g., 1.25 mmoles), without pre-drying, was oxidized with potassium permanganate in the usual manner. After acidification with sulfur dioxide, the crude reaction product (5 g.) was esterified with diazomethane and chromatographed on 150 g. of acid washed alumina. Elution with 1.0 l. of 1:1 benzene-ether provided 3.5 g. of impure lactone dimethyl ester 43c from which the purified sample, m.p. 218-20 C, was obtained by recrystallization from benzene-pentane.

Elution with chloroform (0.5 l.) and 2% methanol in chloroform (1 l.) provided the crystalline hydroxy ester (1.3 g.). $\checkmark_{\text{max}}$

3540 (m), 1789 (s), 1732 cm^{-1} (s). The compound was not characterized further because of the failure to obtain it in a purified state.

b) Hydrogenolysis of the unsaturated lactone dimethyl ester 50b.

The unsaturated lactone dimethyl ester (0.208 g., m.p. 182-84 C) was dissolved in 4 mls. of glacial acetic acid containing 46 mgs. of platinum oxide and hydrogenolized at 700 p.s.i and 120 C for 26 hours. Filtration and recrystallization from glacial acetic acid gave methyl maleopimarate (28b), m.p. 216-18 C, the infrared spectrum (nujol mull) of which was identical with that of authentic anhydride 28b.

c) Ozonation of the unsaturated lactone dimethyl ester 50b.

The lactone dimethyl ester (3.04 g.) was dissolved in ethyl acetate (70 mls.) and a stream of ozone in air (dried at -70 C) passed through the solution for 90 minutes at -70 C. Removal of the solvent and two recrystallizations from methanol yielded 1.3 g. of the oxido lactone 51, melting point 145-47 C. Recrystallization from dilute methanol solution provided a second crystalline modification, melting point 156-58 C. Calc. for $\text{C}_{26}\text{H}_{36}\text{O}_7$: C, 67.79; H, 7.88; O, 24.31%. Found: C, 67.72; H, 7.51; O, 24.74%. Infrared spectrum: $\checkmark_{\text{max}}^{\text{CHCl}_3}$ 1780 (s), 1740 (s), 1724 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.06 (3H), 8.81 (3H), 8.61 (3H), 8.57 (3H), 7.45 (1H), 6.87 (1H), 6.34(3H), 5.70 (1H).

d) Conversion of the oxido lactone 51 to the hydroxy dilactone 52.

The oxido lactone (1.13 g.) was dissolved in 80 mls. of 1:1

aqueous dioxane containing three drops of perchloric acid and heated on the steam bath for 7 hours. The solvent was then evaporated, the residue washed with water and recrystallized once from methanol, providing 0.90 g. of the hydroxy dilactone 52 as short needles, melting point $340-48^{\circ}\text{C}$ (decomposition). The analytical sample, m.p. $345-49^{\circ}\text{C}$ with prior decomposition, was prepared by recrystallization from methanol and 95% ethanol. Calc. for $\text{C}_{25}\text{H}_{34}\text{O}_7$: C, 67.23; H, 7.68; O, 25.08%. Found: C, 66.86; H, 7.50; O, 25.49%. Infrared spectrum: $\sqrt{\text{nujol}}_{\text{max}}$ 3435 (broad), 1773 (s), 1747 (s), 1720 cm^{-1} (s). Nuclear magnetic resonance spectrum ($\text{CF}_3\text{CO}_2\text{H}$): τ 9.25 (3H), 9.07 (3H), 8.78 (3H), 8.63 (3H), 7.65 (1H, $J = 10\text{ c.p.s.}$), 7.52 (1H), 6.90 (1H, $J_1 = 10\text{ c.p.s.}$, $J_2 = 2\text{ c.p.s.}$), 6.54 (3H), 5.51 (1H).

e) Stability of the hydroxy dilactone 52 towards diazomethane, periodic acid and POCl_3 in pyridine.

A sample of the hydroxy dilactone was dissolved in methanol, ethereal diazomethane added and the solution allowed to stand overnight at 0°C . Evaporation of the solvent and recrystallization from 95% ethanol yielded short needles, melting point $335-40^{\circ}\text{C}$, undepressed on admixture with starting material.

The hydroxy dilactone (0.056 g., 0.117 mmoles) was dissolved in 20 mls. of dioxane. Periodic acid (0.04 g., 0.18 mmoles) in 0.75 mls. of water was then added and the solution stirred at room temperature for 18 hours. The residue obtained after evaporation of the solvent and washing with water, melted at ca. 325°C . The infrared

spectrum (nujol mull) was identical with that of starting material.

The hydroxy dilactone 52 (0.017 g.) was dissolved in 5 mls. of pyridine, 1 ml. of POCl_3 added and the solution stirred at room temperature for 12 hours. The residue obtained after evaporation of the solvent and washing with water melted at $295\text{-}305^\circ\text{C}$. The infrared spectrum (nujol mull) was identical with that of the starting material.

f) Baeyer-Villiger oxidation of the methyl ketone 38.

(i) Preparation and characterization of the methyl ketone.

In an early experiment 25 g. (0.054 moles) of the cis trimethyl ester 34 were dissolved in 150 mls. of glacial acetic acid and a slow stream of air containing ca. 3% ozone passed through the solution at room temperature for 12 hours. The solution was then diluted with water, extracted with ether and the ether solution washed with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. The oily residue was refluxed in 200 mls. of methanol containing 6 mls. of glacial acetic acid and 8 g. of Girard's T reagent for 1 hour. The solution was then concentrated, ether (300 mls.) added and the ethereal solution extracted with 0.5 l. of water. The aqueous layer was refluxed with 15 mls. of conc. HCl for 15 minutes, the precipitated methyl ketone filtered (4.0 g., 16% yield) and recrystallized from methanol (melting point, $168\text{-}68.5^\circ\text{C}$; reported $168\text{-}69^\circ\text{C}$). Calc. for $\text{C}_{26}\text{H}_{36}\text{O}_7$: C, 67.80; H, 7.88; O, 24.32%. Found: C, 67.36; H, 7.47; O, 25.17%. Infrared spectrum: $\checkmark_{\text{max}}$ 1750 (s), 1722 (s), 1667 (s), 1610 cm^{-1} (w). Nuclear magnetic resonance spectrum: γ 9.49 (3H), 8.86 (3H), 7.64 (3H),

6.51 (3H), 6.45 (3H), 6.34 (3H), 3.22 (1H). Ultraviolet spectrum: λ_{max} 305 m μ ($\epsilon = 65$), 240 m μ ($\epsilon = 11,000$). RD in methanol ($C = 0.26$) positive Cotton effect curve $[\alpha]_D -9^\circ$; $[\alpha]_{500} -9^\circ$; $[\alpha]_{400} +23^\circ$; $[\alpha]_{350} +188^\circ$; $[\alpha]_{330} +318^\circ$ (max); $[\alpha]_{290} +21^\circ$ (min); $[\alpha]_{250} +323^\circ$.

The ethereal solution from which the Girard T derivative had been removed by aqueous extraction, was concentrated, a small volume of methanol added and crystallization induced by scratching. Filtration of the precipitate and recrystallization from methanol and ethyl acetate provided ca. 35 mgs. (0.14% yield) of crystals, melting point 195-96 C, shown to be the bicyclic ketone 59 by m.p., mixture melting point, infrared, n.m.r. and RD spectral comparison with a sample prepared by oxidation of the methyl ketone with hydrogen peroxide in $\text{BF}_3 \cdot \text{etherate}$.

In a later experiment 300 g. (0.65 moles) of the cis trimethyl ester 34 in 1.5 l. of glacial acetic acid was ozonized and the formation of methyl ketone 38 followed by the development of ultraviolet absorption at 240 m μ . After 54 hours this absorption had reached a maximum ($\epsilon = 6500$); the reaction was then stopped and the methyl ketone isolated via the Girard T derivative in a 40% yield. The non-ketonic mother liquors, on standing at room temperature, precipitated a small amount of crystalline material, melting point 336-38°C after recrystallization from methanol, shown to be the hydroxy dilactone 52 by infrared spectral comparison with the sample obtained from the oxido lactone 51. On prolonged standing the oil precipitated a small amount of an unidentified

compound which was separated mechanically. $\checkmark_{\text{max}}^{\text{CHCl}_3}$ 3614 (sharp), 3440-50 (broad), 1774 (s), 1718 and 1713 (s), 1664 cm^{-1} (w).

The methyl ketone 38 (1.7 g., 0.0037 moles) was refluxed for 6 hours in 140 mls. of 1:2 aqueous methanol containing 0.33 g. (0.0083 moles) of sodium hydroxide. The solution was then concentrated, acidified and extracted with chloroform. The solution was dried over anhydrous magnesium sulfate, evaporated, and the residual oil (1.8 g.) recrystallized from ethyl acetate to provide the analytical sample of the monoacid 56a, melting point $230-31^{\circ}\text{C}$ (reported $226-28^{\circ}\text{C}$). Calc. for $\text{C}_{25}\text{H}_{34}\text{O}_7$: C, 67.23; H, 7.68; O, 25.08%. Found: C, 67.87; H, 7.72; O, 25.06%. Infrared spectrum: $\checkmark_{\text{max}}^{\text{CHCl}_3}$ 3400-2500 (broad), 1700-1730 (s), 1660 (s) and 1610 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ 9.49 (3H), 8.85 (3H), 7.64 (3H), 6.37 (3H), 6.31 (3H), 3.02 (1H).

Esterification with ethereal diazomethane provided the corresponding oily trans trimethyl ester 56b. Infrared spectrum: $\checkmark_{\text{max}}$ 1730 (sh), 1720 (s), 1660 (s), 1610 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ 9.49 (3H), 8.86 (3H), 7.67 (3H), 6.40 (3H), 6.31 (3H), 6.27 (3H), 3.16 (1H).

Approximately 75 mgs. (0.016 moles) of the trimethyl ester 56b was heated in an evacuated sealed tube at $255-260^{\circ}\text{C}$ for 80 minutes. The sublimed material (4 mgs., 18% yield) was shown to be dimethyl fumarate by comparison of its infrared spectrum with that of authentic material.

g) Attempted Birch reduction of the methyl ketone 38.

The methyl ketone (10.0 g., 0.022 moles) was dissolved in 45 mls. of tetrahydrofuran (distilled from LiAlH_4), the solution then added to ca. 225 mls. of liquid ammonia and lithium metal added in portions over a twenty minute period until a permanent blue color was developed. The solution was allowed to stand at its boiling point for 10 minutes after which excess lithium was destroyed with ammonium chloride and the ammonia evaporated by application of a warm water bath to the reaction flask. Water was added to the residue and the neutral organic products dissolved in chloroform. The solution was dried over anhydrous magnesium sulfate, filtered, evaporated, and the oily residue (3.3 g.) chromatographed on 140 g. of neutral alumina (act. I). Elution with benzene (0.3 l.), ether (0.3 l.), and 1:10 chloroform-ether (0.3 l.) did not yield any material. Elution with 1.1 l. of 1:4 and 0.5 l. of 1:1 chloroform-ether yielded a small amount of oily material (total weight $\cong$ 0.4 g.) which was not examined. Elution with 0.2 l. of chloroform provided 0.5 g. of oil and a final fraction obtained with 1:1 methanol-chloroform (0.3 l.) provided an additional 1.4 g. of oily product.

Rechromatography of the chloroform fraction on neutral alumina (elution with 1:1 ether-chloroform) yielded a small amount of the impure C-1 hydroxymethyl ketone 57 as a pale yellow oil. Infrared spectrum: $\checkmark_{\text{max}}$ 3638 (sharp), 3450-3550 (w), 1750 (sh), 1735 (s), 1670 (s), 1615 cm^{-1} (w). Nuclear magnetic resonance spectrum (CCl_4): γ 9.48 (3H), 9.31 (3H), 7.72 (3H), 6.53 and 6.51 ($\sim$ 6H), 3.19 (1H).

The acidic products of the lithium-ammonia reduction were recovered by acidification of the aqueous layer and extraction with chloroform. The oily residue (1.5 g.) obtained by evaporation of the solvent was esterified with diazomethane and chromatographed on 30 g. of neutral alumina. Elution with ether (0.35 l.) and 1:10 chloroform-ether (0.35 l.) provided crystalline material, melting point 150-60 C after one recrystallization from methanol, shown to be starting material by its infrared spectrum.

h) Reduction of methyl fumaropimarate (42) with lithium in liquid ammonia.

The diacid 42 (10 g., 0.023 moles) was suspended in 600 mls. of tetrahydrofuran-liquid ammonia (1:2) and 600 mgs. of lithium metal added in portions over a 15 minute period until a permanent blue color was developed. After two hours at the boiling point of the solvent, excess lithium metal was destroyed with methanol and the ammonia allowed to evaporate. The residue was acidified with aqueous HCl and the organic material extracted several times with chloroform. The combined chloroform extracts (0.40 l.) were dried over anhydrous magnesium sulfate, filtered and evaporated. One recrystallization of the residual foam (10.6 g.) from ether provided the impure hydroxymethyl diacid 58a, melting point 180-95°C, solidifying and remelting at 254-64°C. The analytical sample, melting point 258-63°C, was prepared by repeated recrystallization from ethyl acetate and methanol-water followed by drying under vacuum at 100°C for 42 hours. Calc. for $C_{24}H_{36}O_5$:

C, 71.25; H, 8.97; O, 19.78%. Found: C, 70.37, H, 8.96; O, 20.13%.

A portion of the hydroxy diacid 58a was esterified with ethereal diazomethane to give the oily dimethyl ester 58b. Infrared spectrum: $\checkmark_{\max}$ 3640 (sharp), 3550 (broad), 1725 (s), 1644 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ 9.39 (3H), 9.25 (3H), 8.91 (6H, $J = 7$ c.p.s.), 6.37 (3H), 6.28 (3H), 4.60 (1H).

60 mgs. of the hydroxy dimethyl ester 58b was allowed to stand at room temperature in 6 mls. of 1:2 acetic anhydride-pyridine for 26 hours. Ether was then added, the solution washed repeatedly with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated to give 55 mgs. of the oily acetate. Infrared spectrum: $\checkmark_{\max}$ 1740 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.39 (3H), 9.19 (3H), 8.92 (6H, $J = 7$ c.p.s.), 7.97 (3H), 6.37 (3H), 6.27 (3H), 4.66 (1H).

j) Preparation of the hydroxymethyl diacid 58a from the dimethyl ester 36.

The hydroxymethyl dimethyl ester 36 (0.30 g., 0.007 moles) was refluxed for 3.5 hours in 75 mls. of aqueous methanol (1:2) containing 2.5 g. (0.062 moles) of sodium hydroxide. The solution was then concentrated, acidified with aqueous hydrochloric acid, the crystalline product filtered, washed with water and recrystallized repeatedly from ethyl acetate and methanol-water to give the hydroxymethyl diacid 58a, melting point $258-63^{\circ}\text{C}$, undepressed on admixture with the sample prepared from the lithium-ammonia reduction of the diacid 42. This correlation

was confirmed by the fact that the infrared spectra of the corresponding dimethyl esters 58b were completely superimposable upon each other. The infrared spectra of the diacids themselves (nujol mull), although similar in broad outline, were definitely not identical, probably because of differing crystalline forms.

k) Baeyer-Villiger oxidation of the methyl ketone 38 with 90% hydrogen peroxide in boron trifluoride-etherate.

The oxidizing reagent was prepared by adding 4.0 g. of 90% hydrogen peroxide to 36 g. of redistilled boron trifluoride-etherate. A portion of this solution (9.2 g., 0.024 moles of H_2O_2) was added with stirring over a five minute period to a solution of the methyl ketone 38 (6.0 g., 0.013 moles) in 100 mls. of tetrahydrofuran the reaction temperature being kept at $25^\circ \pm 2^\circ \text{C}$ with periodic application of an ice bath. After $1\frac{3}{4}$ hours an additional 3.3 g. of H_2O_2 in boron trifluoride-etherate (0.009 moles of H_2O_2) was introduced and stirring continued for two hours. The solution was then poured into water and washed three times with benzene. The combined benzene extracts were washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The partially crystalline residue, after one recrystallization from ethyl acetate, yielded 2.8 g. (48% conversion) of the impure bicyclic ketone 59. The analytical sample, melting point $195-96^\circ \text{C}$, was prepared by additional recrystallization from ethyl acetate and benzene-Skellysolve B. Calc. for $\text{C}_{24}\text{H}_{34}\text{O}_7$: C, 66.33; H, 7.89; O, 25.77%. Found: C, 66.44; H, 7.95; O, 25.76%. Infrared spectrum: $\checkmark_{\text{max}}$

1750 (s), 1720-28 (s), 1410 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.16 (3H), 8.86 (3H), 6.8-7.5 (5H), 6.40 (3H), 6.38 (3H), 6.34 (3H). Ultraviolet spectrum: λ_{max} 284 $\text{m}\mu$ ($\epsilon=28$). RD in methanol ($C=0.144$) negative Cotton effect curve $[\alpha]_D -135^\circ$, $[\alpha]_{500} -162^\circ$, $[\alpha]_{350} -389^\circ$, $[\alpha]_{300} -945^\circ$ (trough), $[\alpha]_{265} +139^\circ$ (peak), $[\alpha]_{250} -250^\circ$.

1) Epimerization of the bicyclic ketone 59 to the exo epimer 60.

The bicyclic ketone 59 (1.0 g., 0.0023 moles) was refluxed for 4 hours in 75 mls. of aqueous-methanol (1:2) containing 8.5 g. (0.21 moles) of sodium hydroxide. The solution was then concentrated at the steam bath and acidified with aqueous HCl. The impure triacid was collected by filtration, washed with aqueous sodium chloride solution and dried under vacuum at 80°C (wt. 1.1 g.). Infrared spectrum: $\checkmark_{\text{max}}^{\text{nujol}}$ 3300-2500 (broad), 1705 (s), 1406 cm^{-1} (m).

Esterification of the keto triacid in T.H.F. with ethereal diazomethane provided the corresponding keto trans trimethyl ester 60, melting point $150-50.5^\circ\text{C}$ after recrystallization from ethyl acetate and methanol. Calc. for $\text{C}_{24}\text{H}_{34}\text{O}_7$: C, 66.33; H, 7.88; O, 25.77%. Found: C, 66.12; H, 7.64; O, 25.88%. Infrared spectrum: $\checkmark_{\text{max}}$ 1732 (sh), 1722 (s), 1408 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.20 (3H), 8.87 (3H), 7.59 (2H), 7.24 (1H, 2 doublets; $J_1 = 5$ c.p.s., $J_2 = 2.5-3$ c.p.s.), 7.11 (1H, broad doublet; $J = 7.5$ c.p.s.), 6.79 (1H, 2 triplets; $J_1 = 7.5$ c.p.s., $J_2 = J_3 \approx 1.7$ c.p.s.), 6.34 (3H), 6.31 (3H), 6.27 (3H). Ultraviolet spectrum: λ_{max} 290 $\text{m}\mu$ ($\epsilon=33$).

R.D. in methanol ($C = 0.232$) $[\alpha]_{700} -33$, $[\alpha]_D -45$, $[\alpha]_{500} -66$,
 $[\alpha]_{400} -97$, $[\alpha]_{350} -110$, $[\alpha]_{324} 0$, $[\alpha]_{317} +105$ (max),
 $[\alpha]_{300} -210^\circ$.

m) Meerwein Ponderff-Verly reduction of the keto trans trimethyl ester.

The keto trimethyl ester 60 (101 mgs., 0.232 mmoles) was dissolved in 35 mls. of isopropanol (distilled from calcium turnings), 500 mgs. (2.42 mmoles) of aluminium isopropoxide added and the solution refluxed for 30 minutes. Slow distillation of the solvent through a Vigreux column was then commenced and continued for 8.5 hours with periodic addition of fresh isopropanol. The solution was then concentrated, dilute aqueous HCl added and the organic product extracted several times with chloroform. The combined extracts were washed with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. The oily residue (95 mgs.) possessed the following spectral properties. Infrared spectrum: $\checkmark_{\max}$ 3625 (sharp), 3530 (broad), 1720 (s), 1388 (m), 1372 cm^{-1} (m). Nuclear magnetic resonance spectrum (CCl_4): τ 8.89, 8.78 ($J = 7$ c.p.s.), 8.76 ($J = 7$ c.p.s.), 6.36, 5.94.

The reduction product was dissolved in 15 mls. of methanol containing 4.35 mmoles of sodium methoxide, refluxed for 90 minutes, then concentrated and acidified with dilute aqueous HCl. The organic product was collected in three ether washes which were then combined, dried over anhydrous magnesium sulfate, filtered, treated with ethereal diazomethane and evaporated. The oily hydroxy trimethyl ester 61 was

homogeneous to two dimensional t.l.c. analysis (alumina) but could not be recrystallized from ethyl acetate, methanol, ethyl ether, CCl_4 , benzene or benzene-Skellysolve. Infrared spectrum: $\bigvee_{\text{max}} 3625$ (sharp), 3540 cm^{-1} (broad). Nuclear magnetic resonance spectrum(CCl_4): τ 8.92 (3H), 8.88 (3H), 7.96 (1H), 7.70 (1H), 7.28 (2H), 6.35 (6H), 6.32 (3H), 5.97 (1H, broad).

n) Reduction with sodium borohydride.

The keto trimethyl ester 60 (0.217 g., 0.50 mmoles) was refluxed for 9 hours in 10 mls. of methanol containing ca. 0.2 g. of sodium hydroxide and an excess of sodium borohydride. The solution was then concentrated, dilute HCl added, and the organic precipitate collected by extraction into ether. The ether solution was then washed with distilled water, dried over anhydrous magnesium sulfate, filtered, evaporated and the colorless foam (190 mgs.) esterified with diazomethane. The infrared spectrum of the oily reduction product was similar to that of the aluminium isopropoxide reduction product. Thin layer chromatographic analysis however clearly showed the presence of a second compound.

160 mgs. of the reduction product was allowed to stand at room temperature in 6 mls. of acetic anhydride-pyridine (1:2) for 28 hours after which water was added and the organic precipitate extracted with benzene. The benzene solution was washed repeatedly with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The oily acetate mixture possessed the following spectral properties. Infra-

red spectrum: $\checkmark_{\max}$ 1720-1730 cm^{-1} (s). Nuclear magnetic resonance spectrum (CCl_4): τ 8.98 (3H), 8.88 (3H), 8.00 and 7.96 (3H), 6.34 (9H), 5.15-5.35 (1H). The acetate mixture was recovered unchanged from vacuum distillation at $180 \pm 5^\circ\text{C}$ over a 12 hour period.

IV. C-1 GEM DIMETHYL SERIES. CORRELATION OF ATISINE WITH THE RESIN ACIDS.

a) Preparation of abieta-7,14 (9)-diene (27e) from methyl abietate (27b).

(i) Reduction of methyl abietate to abietinol (27c).

Commercial methyl abietate (Eastman Distillation Products) was shown by n.m.r. analysis to contain ca. 25% aromatic material (signals at τ 9.19, 9.00 ($J = 6.5$ c.p.s.), 8.84, 8.76, 6.39 (3H), 4.3-4.8 ($\sim 1.4\text{H}$), 3-3.3 ($\sim 0.7\text{H}$)).

1.0 kg. of the commercial material (3.18 moles) was dissolved in 6 l. of anhydrous ether, 73 g. of LiAlH_4 (1.93 moles, 18% excess) dissolved in 1 litre of ether, added with stirring over a period of $3\frac{1}{2}$ hours and stirring continued at room temperature for 4 hours. Excess reagent was then destroyed with ethyl acetate, this was followed by the addition of water (72 mls.), 15% aqueous sodium hydroxide (70 mls.) and finally by a further 210 mls. of water. The solution was then filtered, the ethereal filtrate separated from the aqueous layer and concentrated to give the impure abietinol (815 g., 90% yield) as a pale yellow oil. Infrared spectrum: $\checkmark_{\max}$ 3640 cm^{-1} (sharp). Nuclear magnetic resonance spectrum (CCl_4) 9.18, 9.00 ($J = 6.5$ c.p.s.), 8.84, 8.74, 4.2-4.8, 2.9-3.3.

(ii) Preparation of abietinal semicarbazone.

Chromium trioxide (280 g., 2.8 moles) was added with stirring during a period of 75 minutes to 3.0 l. of pyridine (K.F. reagent) in a 5 l., 3-neck round bottom flask equipped with a mechanical stirrer. Abietinol (251 g., 0.87 moles) in 1.0 l. of pyridine (K.F. reagent) was then added rapidly and stirring continued for 90 minutes. The reaction temperature during formation of the pyridine-chromium trioxide complex and in the subsequent oxidation was kept between 20° and 25° C by the periodic application of an ice-water bath. At the end of this period, excess oxidant was destroyed with 200 mls. of methanol (stirring for 10 minutes), the inorganic precipitate filtered and washed with ether. The ether filtrate was washed successively with aqueous HCl, distilled water, dilute aqueous sodium hydroxide and finally again with distilled water. The solution was then dried over anhydrous magnesium sulfate, filtered and evaporated.

The impure abietinal (27c), obtained as an amber colored oil, possessed the following spectral properties. Infrared spectrum: $\nu_{\max}$ 2695 and 2685 (m), 1725 cm^{-1} (s). Nuclear magnetic resonance spectrum (CCl_4): τ 9.17, 9.00 ($J = 6.5$ c.p.s.), 8.87, 8.74, 4.3-4.9, 2.7-3.3, 1.45, 0.85.

A buffered solution of semicarbazide was prepared by dissolving 125 g. of the corresponding HCl salt in 300 mls. of methanol containing 140 g. of sodium acetate. The solution was filtered free of sodium chloride and immediately added to the crude abietinal. The reaction

temperature during semicarbazone formation was kept in the range 20-25°C with an ice-water bath. Filtration provided 123 g. (42% yield) of impure abietinal semicarbazone as a pale yellow amorphous solid, melting point 207-222°C (reported 215°C). Infrared spectrum: $\checkmark_{\text{max}}^{\text{CHCl}_3}$ 3540 (m), 3480 (w), 3418 (w), 3362 (w), 1685 (s), 1570 cm⁻¹ (s). Ultra-violet spectrum: λ_{max} 234 m μ .

(iii) Wolff-Kishner reduction of abietinal semicarbazone.

A solution of potassium hydroxide (45 g., 0.80 moles) in 950 mls. of diethylene glycol was heated to 190 C. After 15 minutes the expulsion of water had ceased and abietinal semicarbazone (87 g., 0.254 moles) was added. The solution was stirred for 5.5 hours at 190 C under a nitrogen blanket, then cooled, diluted with water and extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to a small volume. Vacuum distillation of the dark brown residue (65 g., 92% yield) provided 51.4 g. (74% yield) of the hydrocarbon mixture, b.p. 130-150 C (0.05-0.10 mm.). Infrared spectrum: $\checkmark_{\text{max}}$ 3080 (w), 1630 (w), 1495 cm⁻¹ (w). Nuclear magnetic resonance spectrum (CCl₄): τ 9.22, 9.00 (J = 6.5 c.p.s.), 8.84, 8.74, 4.25-4.8, 3.0-3.3.

The integrated absorption intensities of the olefinic and aromatic regions were in the ratio of 6:5 indicating a mixture of ca. 62% abieta 7,14 (9)-diene (27e) and 38% of the aromatic hydrocarbon 62d.

b) Preparation of abieta 7,14 (9)-diene from rosin.

Rosin (150 g., 0.5 moles) dissolved in 500 mls. of anhydrous

ether was added with stirring over a four hour period to a solution of 17 g. (0.45 moles) of LiAlH_4 in 500 mls. of anhydrous ether contained in a 2 l. round bottom flask equipped with a reflux condenser and addition funnel. After stirring for 18 hours at room temperature, ethyl acetate (25 mls.), water (17 mls.), 15% aqueous sodium hydroxide (17 mls.) and water (50 mls.) were added in that order. The solution was then filtered, washed with aqueous sodium hydroxide and concentrated. The dark residual oil, obtained in a 63% yield, showed the expected infrared absorption at ν_{max} 3640 (sharp), 3400 (broad).

The preparation of abietinol, without purification, was converted to the hydrocarbon mixture as described in part a. Nuclear magnetic spectral analysis of the undistilled product indicated a mixture of ca. 84% diene and 12% of the aromatic hydrocarbon (62d). Infrared spectrum: ν_{max} 3080 (w), 1635 (w) and 1495 cm^{-1} (w). Nuclear magnetic resonance spectrum (CCl_4): τ 9.22, 9.13, 9.05, 8.94, 8.84, 8.74, 4.25-4.80, 3.0-3.3. Ultraviolet spectrum: λ_{max} 231, 240, 250 $\text{m}\mu$ (sh).

c) Diels-Alder reaction of abieta 7,14 (9)-diene. Preparation of the C-1 gem dimethyl anhydride 30.

A solution of impure abieta 7,14 (9)-diene (20 g., prepared from rosin by procedure b) and 20 g. of maleic anhydride in 20 mls. of p-cymene was heated in a sealed tube at 160 C for 8 hours. The reaction product was then diluted with benzene, heated briefly on the steam bath with 100 mls. of aqueous sodium hydroxide and the sodium salt of the

desired adduct 30, obtained as a tan colored gum after filtration. The sodium salt was suspended in dioxane, acidified with aqueous HCl and the resulting two phase solution extracted several times with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The oily residue (7.1 g.) was then heated under vacuum at 160 C for 1.5 hours and chromatographed on 400 g. of silica gel. The initial benzene forerun (0.6 l.) contained a negligible amount of material and was discarded. The next five fractions (combined weight; 3.8 g., 14% yield, elution with 0.5 l. of benzene) crystallized from Skellysolve B. Repeated recrystallization from Skellysolve B and from ether provided the analytically pure gem dimethyl adduct 30, melting point 109.5-110.5 C. Calc. for $C_{24}H_{34}O_3$: C, 77.78; H, 9.26%. Found: C, 77.72, H, 9.04%. Infrared spectrum: $\checkmark_{\max}$ 1850 (m), 1770 (s), 1630 cm^{-1} (w). Nuclear magnetic resonance spectrum: γ 9.42 (3H), 9.18 (3H), 9.09 (3H), 8.99 (6H, $J = 7\text{ c.p.s.}$), 6.8-7.0 (2H, complex), 4.41 (1H).

The gem dimethyl anhydride 30 (0.76 g., 0.0021 moles) was converted to the dimethyl ester 63, melting point 124-25 C after recrystallizing from Skellysolve B and ethyl acetate, by refluxing in methanol for 1.5 hours followed by esterification with diazomethane and filtration through a column of acid washed alumina (20 g.).

The following procedure for forming and isolating the Diels-Alder adduct 30 was developed after several unsuccessful attempts were encountered in attempting to apply the above procedure to the hydrocarbon

mixture obtained from methyl abietate.

Impure abieta 7,14 (9)-diene (78.8 g., 0.29 moles), obtained by reduction of methyl abietate, and an equal weight of maleic anhydride were placed in a 250 ml. round bottom flask, the system flushed with nitrogen, stoppered and heated at 150° C for 5 hours. The reaction mixture was then cooled, diluted with benzene, washed several times with water and shaken with dilute aqueous sodium hydroxide for two hours. The light yellow gum which formed during this period was collected by filtration and dissolved in tetrahydrofuran. The sodium salt crystallized from solution on standing overnight at room temperature. The yield, after drying under vacuum at 50 C for 3 hours, was 13.1 g. (10.5% conversion).

The sodium salt was converted to the dimethyl ester 63 by either one of the two following procedures.

(i) A suspension of the sodium salt (23.7 g., 0.055 moles) was refluxed for 15 hours in 1 l. of anhydrous methanol containing 30 g. of anhydrous HCl gas. The solvent was then removed by distillation, benzene added, the solution washed several times with water, dried over anhydrous magnesium sulfate, filtered and concentrated. The residual oil crystallized on seeding with the dimethyl ester obtained by esterification of the anhydride 30. The yield of dimethyl ester, melting point 115-20° C was 19.3 g. (85% conversion).

(ii) The sodium salt (0.88 g., 2.0 mmoles) was suspended in 50 mls. of methanol containing 2.4 mls. (24 mmoles) of dimethyl-

sulfate and stirred at room temperature for $2\frac{3}{4}$ hours. The solvent was then removed under reduced pressure, benzene added and the solution washed several times with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residual yellow oil showed weak infrared absorption at 1770 and 1840 cm^{-1} (anhydride) and so was dissolved in methanol and treated with diazomethane. Evaporation of the solvent and filtration through a short column of acid washed alumina provided 0.60 g. (75% yield) of the crystalline dimethyl ester 63 identified by its infrared spectrum.

d) Oxidation of the dimethyl ester 63 with ozone.

The dimethyl ester (4.2 g., 0.01 moles) was dissolved in 100 mls. of glacial acetic acid and ozonized at room temperature until the ultraviolet absorption at 240 $\text{m}\mu$ reached a maximum (3.5 hours, $\epsilon = 6,400$). The solution was then diluted with water and extracted twice with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residual oil was refluxed for 45 minutes in 50 mls. of methanol containing 2 mls. of acetic acid and 3.0 g. of Girard's T reagent, then concentrated, ether added and extracted twice with water. The combined aqueous extracts were acidified with 5 mls. of conc. HCl and heated on the steam bath for 10 minutes. The organic precipitate was extracted into benzene, washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization of the solid residue (1.2 g., 30% yield) from methanol and benzene-Skellysolve B

provided the analytically pure methyl ketone 64, m.p. 167-168 C. Calc. for $C_{25}H_{36}O_5$: C, 72.07; H, 8.72; O, 19.21%. Found: C, 72.27; H, 8.57; O, 18.54%. Infrared spectrum: $\checkmark_{\max}$ 1745 (s), 1730 (sh), 1667 (s), 1610 cm^{-1} (w). Nuclear magnetic resonance spectrum: γ 9.51 (3H), 9.20 (3H), 9.11 (3H), 7.63 (3H), 7.19 (1H, $J=11$ c.p.s.), 6.93 (1H, quartet; $J_1=11$ c.p.s., $J_2=2$ c.p.s.), 6.48 (3H), 6.42 (3H), 3.07 (1H). Ultraviolet spectrum: $\lambda_{\max}$ 310 $m\mu$ ($\epsilon=43$), 240 $m\mu$ ($\epsilon=9,600$). R.D. in methanol ($C=0.206$) positive Cotton effect curve. $[\alpha]_{700}^{+33}$, $[\alpha]_D^{+39}$, $[\alpha]_{500}^{+50}$, $[\alpha]_{400}^{+113^\circ}$, $[\alpha]_{330}^{+460^\circ}$ (peak), $[\alpha]_{297}^{+52^\circ}$ (trough), $[\alpha]_{280}^{+442}$.

e) Baeyer-Villiger oxidation of the methyl ketone 64 with 90% H_2O_2 in boron trifluoride-etherate.

The oxidizing reagent was prepared by adding 4.8 g. of 90% hydrogen peroxide to 36 g. of redistilled boron trifluoride-etherate.

A portion of this solution (12.0 g., 0.036 moles of H_2O_2) was added with stirring over a 15 minute period to a solution of the methyl ketone 64 (5.6 g., 0.0134 moles) in tetrahydrofuran (100 mls.), the reaction temperature being maintained at 20°C by the periodic application of an ice-water bath. After 3 hours the solution was diluted with water and extracted three times with benzene. The combined benzene extracts were washed several times with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residual oil slowly crystallized on standing to provide 2.4 g. (45% yield) of the impure bicyclic ketone 65. The analytical sample, melting point 179-80 C, was

prepared by recrystallization from methanol and benzene-Skellysolve.

Calc. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.78; O, 20.48%. Found: C, 70.72; H, 8.65; O, 20.64%. Infrared spectrum: $\nu_{\max}$ 1750 (s), 1728 (s), 1410 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.17 (6H), 9.12 (3H), 7.5-7.2 ($\sim$ 2H), 7.12 (1H, $J = 2$ c.p.s.), 6.82 (1H, $J = 11.5$ c.p.s.), 6.38 (3H), 6.35 (3H). Ultraviolet spectrum: $\lambda_{\max}$ 284 $m\mu$ ($\epsilon = 28$). R.D. in methanol ($C = 0.188$) negative Cotton effect curve. $[\alpha]_{700} -23$, $[\alpha]_D -51^\circ$, $[\alpha]_{450} -106^\circ$, $[\alpha]_{350} -283^\circ$, $[\alpha]_{298} -940^\circ$ (trough), $[\alpha]_{275} 0$, $[\alpha]_{265} +281^\circ$ (peak), $[\alpha]_{250} 0$.

f) Conversion of the bicyclic ketone 65 to the keto olefin 66.

The bicyclic ketone 65 (2.0 g., 5.1 mmoles) was refluxed in 60 mls. of 40% aqueous methanol containing 0.5 g. of sodium hydroxide for 1 hour. The solution was then cooled, acidified with dilute aqueous HCl and the keto diacid collected by filtration and dried overnight under vacuum at $80^\circ C$, (wt. 1.74 g., 94% yield) melting point $265-80^\circ C$. Infrared spectrum: $\nu_{\max}^{nujol}$ 3100 (broad), 2800-2400 (broad), 1710 (s), 1410 cm^{-1} (m).

The diacid (1.74 g., 4.8 mmoles) was dissolved in 75 mls. of pyridine, lead tetraacetate (1.7 g., 3.84 mmoles) added, and the solution stirred first at $28^\circ C$ for 30 minutes, then at $42 \pm 3^\circ C$ for $1\frac{1}{4}$ hours. An additional 1.1 g. (2.5 mmoles) of lead tetraacetate was then added and stirring continued for 3.5 hours at a temperature of $40 \pm 5^\circ C$. At the end of this period unreacted lead tetracetate was destroyed with ethylene glycol, water added and the organic precipitate extracted with several

portions of benzene. These were combined, washed with 5% aqueous sodium hydroxide and distilled water, then dried over anhydrous magnesium sulfate, filtered and evaporated. The residual oil (0.2 g.) was chromatographed on 5 g. of neutral alumina. Elution with benzene (150 mls.) provided a trace of oil which could not be induced to crystallize. The crystalline keto olefin 66 (50 mgs. 5% yield) was obtained by subsequent elution with 1:1 benzene-ether. Recrystallization from methanol and Skellysolve B provided the purified sample, melting point 123-23.5 C.

Infrared spectrum: $\checkmark_{\max}$ 3030 (w), 3020 (w), 1719 (s), 1407 cm^{-1} (w).

Nuclear magnetic resonance spectrum: τ 9.17 (3H), 9.11 (6H), 7.54 (1H), 7.35 (1H), 6.98 (1H, octet), 3.95 (1H, q., $J_1 = 8$ c.p.s., $J_2 = 6$ c.p.s.), 3.81 (1H, q., $J_1 = 2$ c.p.s.). Ultraviolet spectrum: ($C = 0.0225$)

$\lambda_{\max}$ 294 $m\mu$ ($\epsilon = 140$). R.D. in isooctane ($C = 0.069$). Positive Cotton effect curve $[\alpha]_{700}^{+324}$, $[\alpha]_{600}^{+465}$, $[\alpha]_{500}^{+595}$, $[\alpha]_{400}^{+1305}$, $[\alpha]_{350}^{+3,050}$, $[\alpha]_{316}^{+10,000}$ (peak), $[\alpha]_{320}^{+7750}$, $[\alpha]_{305}^{+8,500}$, $[\alpha]_{284}^0$, $[\alpha]_{280}^{-1,740}$, $[\alpha]_{270}^{-5700}$, $[\alpha]_{265}^{-6,800}$. Mass spectrum: molecular ion at $m/e = 272$. Other peaks at $m/e = 230$ (6.5%), 137 (8.4%), 106 (9.4%).

Unchanged keto diacid was recovered by the following isolation procedure.

The aqueous layer, after extraction of neutral products with benzene, was acidified with dilute HCl and extracted with ether. The ether was then evaporated, acetic acid added, and the insoluble material removed by filtration. The filtrate was acidified with anhydrous HCl and

the lead chloride removed by filtration. Evaporation of the filtrate provided a brown oil from which 0.20 g. of the diacid crystallized on addition of ether. The melting point, after washing with a small volume of benzene, was 265-75°C.

g) Hydrogenation of the keto olefin 66.

The keto olefin 66 (32 mgs., 0.117 mmoles) was dissolved in 25 mls. of methanol containing 14 mgs. of 5% Pd-C and hydrogenated at room temperature and atmospheric pressure for $3\frac{3}{4}$ hours. Filtration and evaporation of the solvent provided a quantitative yield of the dihydroketone 70, melting point 126.5-127°C after recrystallizing from methanol and Skellysolve B. Infrared spectrum: $\checkmark_{\text{max}}$ 1717 (s), 1404 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.21 (3H), 9.19 (3H), 9.12 (3H), 7.71 (1H, quintet), 7.46 (0.5 H, t), 7.26 (0.5H, broad singlet). R. D. in methanol ($C = 0.116$) positive Cotton effect curve. $[\alpha]_{700}^{+34}$, $[\alpha]_{\text{D}}^{+41}$, $[\alpha]_{500}^{+62^\circ}$, $[\alpha]_{400}^{+100^\circ}$, $[\alpha]_{350}^{+117^\circ}$, $[\alpha]_{312}^{+360^\circ}$ (peak), $[\alpha]_{283}^{+29^\circ}$ (trough), $[\alpha]_{250}^{+310^\circ}$. Mass spectrum: molecular ion at $m/e = 274$. Other peaks at 259 (3.6%), 123 (9.3%).

h) Wolff-Kishner reduction of the dihydroketone 70 - Barton modification.

Sodium metal (0.56 g.) was dissolved in diethylene glycol (25 mls.) and anhydrous hydrazine (refluxed over sodium hydroxide pellets) added until the solution refluxed freely at 125°C. Hydrazine was then distilled from the reaction flask until the refluxing temperature had reached 175°C. The dihydroketone (32 mgs.) dissolved in 5 mls. of diethylene

glycol, was introduced and refluxing continued for 11 hours. The reaction temperature was then raised to 210°C by distilling out additional hydrazine and the refluxing continued at this temperature for 11 hours. During these last two operations the hydrocarbon sublimed into the condenser where it was recovered by washing with pentane. The pentane solution was in turn washed repeatedly with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. Several recrystallizations of the solid residue (22 mgs.) provided the pure hydrocarbon 71, melting point $86-86.5^{\circ}\text{C}$. Calc. for $\text{C}_{19}\text{H}_{32}$: C, 87.61; H, 12.39%. Found: C, 87.55; H, 12.28%. Infrared spectrum: $\checkmark_{\text{max}}$ 2850-3000 (s), 1455 (s), 1440 (m), 1385 (s), 1368 (s), 728 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.18 (3H), 9.15 (3H), 9.05 (3H, d., $J \approx 1.2$ c.p.s.). R.D. curve in methanol ($C = 0.044$). Plain positive dispersion curve $[\alpha]_{\text{D}}^{+36^{\circ}}$, $[\alpha]_{500}^{+49^{\circ}}$, $[\alpha]_{400}^{+77^{\circ}}$, $[\alpha]_{350}^{+120^{\circ}}$. Mass spectrum: molecular ion at $m/e = 260$ (2.4%). Other peaks at $m/e = 245$ (3.5%), 175 (2.7%), 123 (7.9%), 109 (3.6%).

An additional 2.5 mgs. of the hydrocarbon 71 was obtained by the following isolation procedure.

The cooled solution was diluted with water and extracted twice with pentane. The combined pentane extracts were washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The crystalline residue (4 mgs.) showed medium intensity absorption at 1717 cm^{-1} and a weak band at 1402 cm^{-1} .

Chromatography on 0.40 g. of neutral alumina (elution with

10 mls. of pentane) provided 2.5 mgs. of the hydrocarbon, melting point 86-87 C after sublimation at 60 C. The identification was confirmed by comparison of its infrared spectrum (semimicro cell) with that of the hydrocarbon described above. The overall yield of hydrocarbon was 24 mgs. (~ 80% conversion).

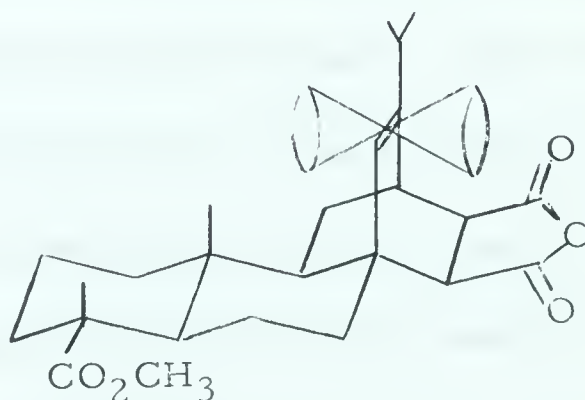
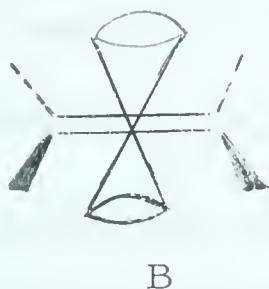
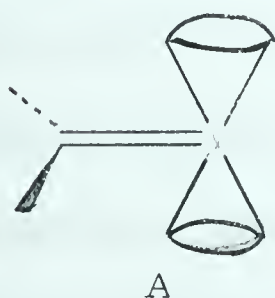
2. ANISOTROPY EFFECTS IN MALEOPIMARIC ACID DERIVATIVES AND SOME TRANSFORMATION PRODUCTS OF THE KETO TRIMETHYL

ESTER 59.

A. INTRODUCTION

These studies were initiated with the intention of developing a method for removing the C-7 keto group in the C-1 gem dimethyl ketone 65 but were later extended in a study of the anisotropy effect of the C-7, C-8 double bond and will be discussed from this point of view.

The unusually high chemical shift value of the C-17 protons in methyl maleopimarate (28b) ($\tau=9.41$) has already been noted and explained by a shielding effect of the C-7, C-8 double bond analogous to that observed for a carbonyl group (see structures A and B) where the only significant difference arises out of the fact that in keto compounds, because of the greater electronegativity of oxygen relative to carbon, the axis of the shielding cone is shifted from a point midway along the double bond to the oxygen itself.



Similar high field signals were observed in all other compounds containing a C-7, C-8 olefinic bond, ranging for the most part from 9.35 to 9.43 τ , but occasionally (as in the methyl ketones 38, 56 and 64 and in the exo methylene dimethyl ester 47) appearing at ca. 9.50 τ (Table III, Type A).

In the several compounds prepared which contained either an isopropylidene group or a carbonyl function at C-7, the angular methyl appeared at 9.23 ± 0.07 (Table III, Type B). The paramagnetic shift accompanying this structural modification was attributed first to the fact that the methyl protons are more remote from the anisotropic group and secondly to the fact that they are also further removed from the axis of the shielding cone (and region of maximum shielding) than in the endo-cyclic compounds.

A third class of compounds (Type C) are devoid of unsaturation at C-7 and are characterized by C-17 methyl absorption at a particularly consistent value of 9.05 τ .

Before proceeding with a discussion of the shielding effects associated with the various C-7 unsaturated systems, attention is drawn to the small solvent effect shown by the carbomethoxyl signals which are invariably located at somewhat higher field in carbon tetrachloride solution than in deuteriochloroform. This effect presumably arises through solvation of the carbonyl group with deuteriochloroform which causes a small inductive withdrawal of electrons at the methoxyl protons. For this reason the n.m.r. spectra have been obtained in deuteriochloroform

and the detailed discussion is restricted to this solvent system.

The enhanced shielding of the C-17 protons in the methyl ketones 38, 56a, 56b and 64 relative to compounds containing an isolated endocyclic double bond can be attributed either to a deshielding effect of the isopropyl group^{103,104} which is removed by oxidation to the ketone or to a greater shielding capacity of the conjugated system.

Similar arguments can be advanced for the high field position of the angular methyl in the exo methylene dimethyl ester 47. Thus, conversion of the axial C-16 methyl to an exo methylene group would be expected to remove a deshielding effect of 0.05-0.10 p.p.m. on the C-17 methyl resulting from their 1,3 diaxial relationship¹⁰⁵ and thereby, if the cis trimethyl ester 34 is employed as a standard ($\tau_{C-17} = 9.38$), lead to a predicted value of 9.43-9.48 τ for the dimethyl ester 47. The fact that this corrected figure is still lower than the observed value of 9.51 τ suggests the possibility of additional shielding by the exo methylene group.

The shielding effect of the eclipsed carbomethoxyl groups each other is best seen by examining the resonance position of the C-22 carbomethoxyl group in a series of closely related compounds. For example in the cis trimethyl ester 34 this signal is located at 6.47 τ whereas in the C-21 exo carboxyl and carbomethoxyl derivatives 41 and 32 it appears at 6.37 and 6.38 τ respectively. In a second comparison the C-22 ester signal of the methyl ketone 38 is found at 6.45 τ and drops to 6.37 and 6.40 τ in the C-21 exo carboxyl and carbomethoxyl derivatives

TABLE III

Anisotropy Effect Associated with C-7 Olefinic and Carbonyl Groups.

Type	Compound	C-17	C-21 CO ₂ CH ₃	C-22 CO ₂ CH ₃	Relative Configurations	C-15 CO ₂ CH ₃
A	methyl maleopimarate 28b	9.41				6.33
	C-1 hydroxymethyl anhydride 35	9.39				
	C-1 acetoxy anhydride 48	9.43				
	C-1 <u>gem</u> dimethyl anhydride 30	9.42				
	C-1 hydroxymethyl lactone 37	9.38				
	<u>cis</u> trimethyl ester 34	9.38	6.47 (6.53) [‡]	6.47 (6.53)	cis	6.33
	C-21 carboxy dimethyl ester 41	9.40	--	6.37	trans	6.30
	<u>trans</u> trimethyl ester 32	9.42	6.27	6.38	trans	6.31
	methyl ketone 38	9.49	6.51 (6.53)	6.45 (6.50)	cis	6.34 (6.36)
	C-21 carboxy methyl ketone 56a	9.49	--	6.37	trans	6.31
	C-21 <u>exo</u> carbomethoxyl ketone 56b	9.49	6.27 (6.26)	6.40 (6.42)	trans	6.31 (6.36)
	C-1 <u>exo</u> methylene dimethyl ester 47	9.51	6.45	6.45	cis	--
	C-1 hydroxymethyl dimethyl ester 36	9.35	6.43 (6.52)	6.43 (6.52)	cis	--
	C-1 hydroxymethyl <u>trans</u> dimethyl ester 58b	9.39	6.28 (6.33)	6.37 (6.44)	trans	--

TABLE III - Continued

Type	Compound	C-17	C-21 CO ₂ CH ₃	C-22 CO ₂ CH ₃	Relative Configurations	C-15 CO ₂ CH ₃
A	C-1 hydroxymethyl <u>trans</u> dimethyl acetate 58c	9.39	6.27 (6.34)	6.37 (6.43)	cis	--
	C-1 <u>gem</u> dimethyl dimethyl ester 63	9.41	6.47 (6.53)	6.47 (6.53)		--
	C-1 <u>gem</u> dimethyl ketone 64	9.51	6.48 (6.52)	6.42 (6.48)		--
	diene 40	(9.38)	--	--		(6.36)
	dihydrodiene 91	(9.42)	--	--		(6.38)
B	isopropylidene lactone 50b	9.26	6.35	--	cis	6.35
		9.30	6.28	--	trans	6.36
	isopropylidene trimethyl ester 45	9.19	6.27	6.30 or 6.32	trans	6.32 or 6.30
	keto trimethyl ester 59	9.16	6.40	6.38	cis	6.34
	keto trans trimethyl ester 60	9.20	6.27 (6.30)	6.31 (6.32)	trans	6.34 (6.37)
C	C-1 <u>gem</u> dimethyl ketone 65	9.17	6.38	6.35	cis	--
	dihydro ketone 70	9.19 or 9.21	--	--		--
	saturated lactone monoester 43b	9.05	--	--	cis	6.33

TABLE III - Continued

Type	Compound	C-17	C-21 CO ₂ CH ₃	C-22 CO ₂ CH ₃	Relative Configurations	C-15 CO ₂ CH ₃
C	saturated lactone dimethyl ester 43c	9.05	--	6.35	cis	6.35
	oxido lactone 5l	9.06	6.32 or 6.34	--	cis	6.34 or 6.32
	hydroxy trimethyl ester 44b	9.05	6.33 or 6.27	6.27 or 6.33	trans	6.33
	hydrocarbon 7l	9.05	--	--	--	--

± shifts in parentheses are for CCl₄ solution.

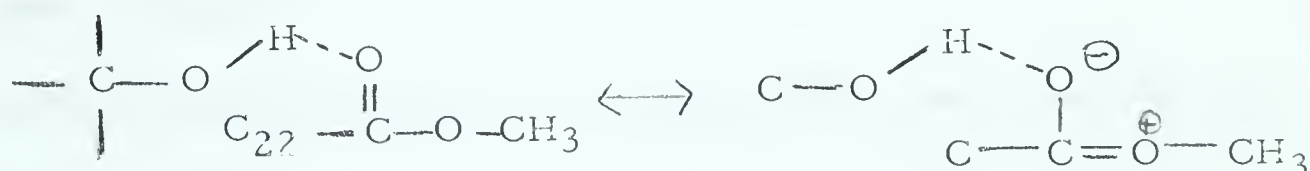
56a and 56b. As a final illustration from the type A compounds the C-22 ester function of the C-1 hydroxymethyl dimethyl ester 36 ($\tau = 6.43$) is to be compared with the trans dimethyl ester 58b and the corresponding acetate 58c in which the C-22 carbomethoxyl signals now appear at 6.37 τ . The B type compounds provide one further example of carbomethoxyl shielding in the epimeric pair of keto trimethyl esters 59 and 60 which possess C-22 ester signals at 6.38 and 6.31 τ respectively.

From the above examples it would appear that epimerization of a C-21 carbomethoxyl group to an exo orientation causes a paramagnetic shift of 0.07 ± 0.02 p.p.m. in the resonance position of the C-22 carbomethoxyl protons. However, inspection of the data also shows that the same process deshields the C-21 carbomethoxyl group to an even greater extent (0.20 ± 0.04 p.p.m. in the four examples referred to above). If it is assumed that the carbomethoxyl functions deshield each other to the same extent it follows that other shielding or deshielding factors must be operative. One very obvious explanation is that an endo C-21 carbomethoxyl group is shielded by the olefinic bond while the exo epimer is either unaffected or possibly even deshielded by it.

Involvement of the double bond as an important part of the molecular environment influencing the resonance position of the C-21 and C-22 carbomethoxyl groups is supported by the observation that in two saturated compounds (Type C; compounds 43c and 44b) the β (or endo) C-22 carbomethoxyl groups possess n.m.r. signals at lower field than the nearest unsaturated analogs 34 and 32 (0.12 and 0.13 p.p.m.

respectively).

Although these figures are in good agreement with each other their reliability as a measure of double bond shielding is open to some criticism. First, with respect to the choice of 43 b as a standard, it must be pointed out that the measured value (0.12 p.p.m.) may contain a shielding or deshielding term resulting from the conversion of the C-21 carbomethoxyl group to a γ lactone. Secondly, in connection with the hydroxy trimethyl ester 44b, attention is drawn to the fact that assignment of the 6.27 τ signal to the C-22 carbomethoxyl group is based on the expectation that the intramolecular hydrogen bond to the ester carbonyl revealed by infrared absorption at 3470 and 1710 cm^{-1} should deshield the methoxyl protons.



A measure of the extent to which this deshielding process occurs, can be obtained by examination of the chemical shift value of the C-22 carbomethoxyl proton in the isopropylidene trimethyl ester 45. Assuming that the influence of an exocyclic double bond is negligible, the difference (0.03 p.p.m.) provides an indication of the extent to which hydrogen bonding contributes to the paramagnetic shift accompanying the trans trimethyl ester 44b conversion. The difference (0.11-0.03=0.08 p.p.m.) can therefore be ascribed to the shielding effect of a C-7, C-8 double bond on the C-22 carbomethoxyl protons.

Returning now to the paramagnetic shifts of the C-21 carbomethoxyl groups which accompany their epimerization to an exo configuration, it is seen that incorporation of the olefinic shielding term still does not account completely for the observed shifts. This fact is best seen by application of equation (1) to the following examples:

$$\Delta\delta_T = \Delta\delta_C + \Delta\delta_O + \Delta\delta_X \quad (1)$$

$\Delta\delta_C$ = mutual shielding of the carbomethoxyl groups, determined in each case by the downfield shift of the C-22 carbomethoxyl signal accompanying epimerization at C-21.

$\Delta\delta_O$ = shielding by the olefinic bond as estimated by comparison of the two saturated compounds 43c and 44b with their unsaturated analogs 34 and 32.

$\Delta\delta_X$ = residual deshielding term accompanying epimerization to an exo position.

(1) cis trimethyl ester 34 $\longrightarrow$ trans trimethyl ester 32

$$0.20 = 0.09 + 0.08 + \Delta\delta_X$$

$$\Delta\delta_X = 0.03 \text{ p.p.m.}$$

(2) C-1 hydroxymethyl dimethyl ester 36 $\longrightarrow$ trans dimethyl ester 58b

$$0.15 = 0.06 + 0.08 + \Delta\delta_X$$

$$\Delta\delta_X = 0.01 \text{ p.p.m.}$$

(3) Analysis of the methyl ketone 38, C-21 exo carbomethoxyl ketone 56b transformation is complicated by the abnormally high field location (6.51 τ) of the endo C-21 ester group which

presumably arises from its proximity to the keto group.

Taking its resonance position after correction for this effect as being identical with that of the C-22 carbomethoxyl group, the following analysis is possible:

$$0.18 = 0.06 + 0.08 + \Delta\delta_X$$

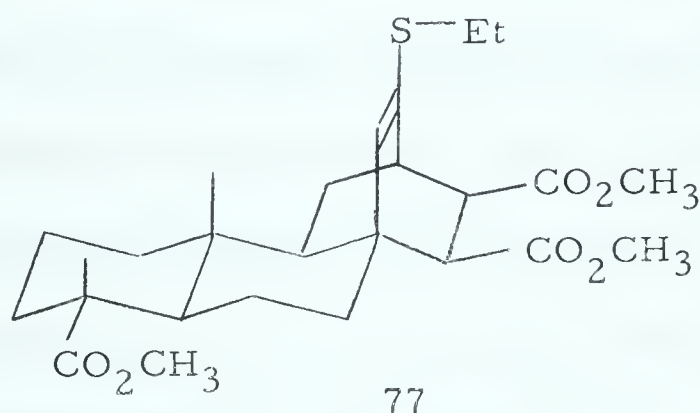
$$\Delta\delta_X = 0.04 \text{ p.p.m.}$$

Although these examples suggest that the introduction of a C-7, C-8 double bond will deshield a C-21 exo carbomethoxyl group, the validity of the conclusions depends on a questionable calculation of $\Delta\delta_O$ for the endo C-22 ester function as well as on the assumption that these values ($\Delta\delta_O$ and $\Delta\delta_C$) are applicable to the C-21 carbomethoxyl group.

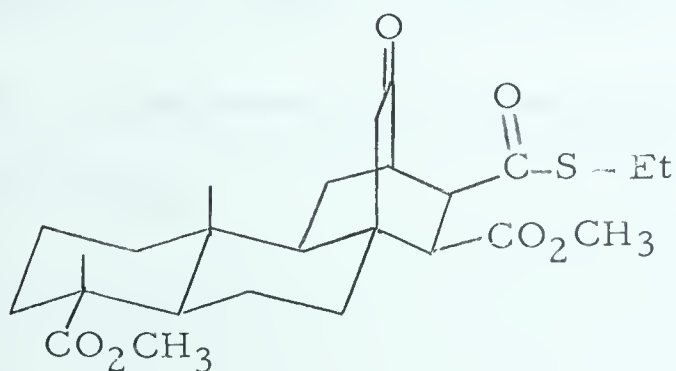
In the investigations which are now described, n.m.r. data is presented which permits a direct measurement of $\Delta\delta_O$ for an endo C-21 ester function and provides evidence for a deshielding effect of the olefinic double bond on an exo C-21 carbomethoxyl group. In addition, the results show that the C-17 methyl protons are not deshielded by the isopropyl group, thereby indicating that their shift to higher field in the methyl ketones probably derives from an enhanced shielding ability of the conjugated system.

B. RESULTS AND DISCUSSION

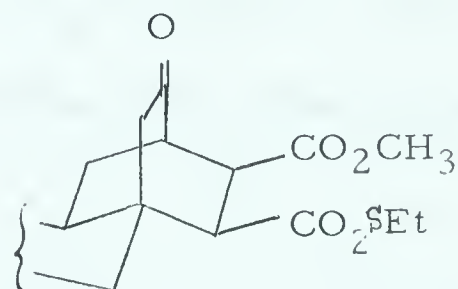
Reaction of the bicyclic ketone 59 with ethyl mercaptan and boron trifluoride-etherate at room temperature for 15 minutes provided an oily product showing two spots on t.l.c. analysis. The presence of signals in the n.m.r. spectrum at 9.34τ (3H) and 8.68τ ($J = 7$ c.p.s.; $\text{CH}_3\text{---CH}_2\text{---S}$) indicated formation of the vinyl sulfide 77 as the major product.



A small amount of crystalline by-product 78, $\text{C}_{25}\text{H}_{36}\text{O}_6\text{S}$, m.p. $207\text{--}09^\circ\text{C}$ was obtained by triturating the oil with ether. The presence of the keto group was indicated by medium intensity infrared absorption at 1405 cm^{-1} and the C-17 methyl group by a signal at 9.18τ in the n.m.r. spectrum. The presence of a thiolic ester function was indicated by an infrared band at 1670 cm^{-1} ¹⁴⁶ and ultraviolet absorption at $238\text{ m}\mu$ ($\epsilon = 2,400$).

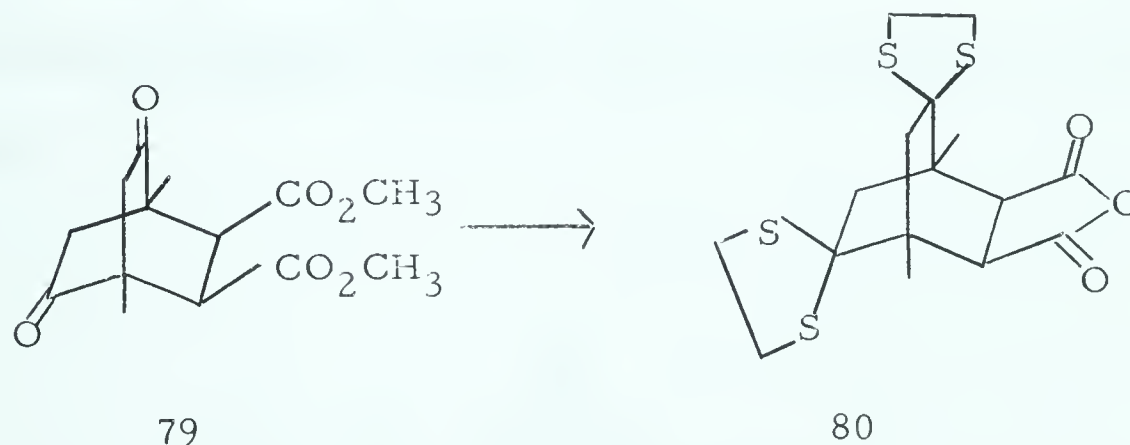


or

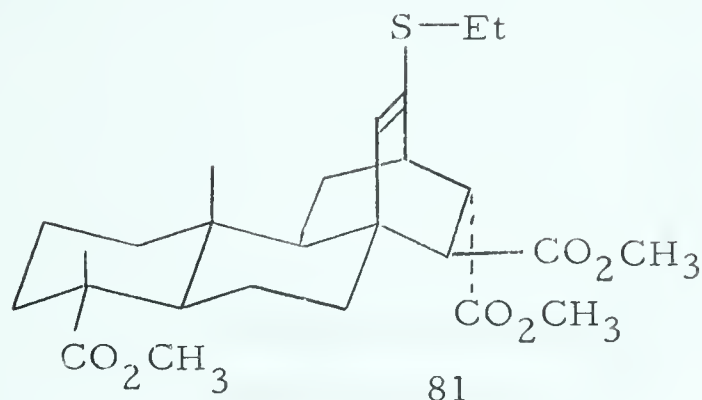


A second side reaction, which appeared to involve both the C-21 and C-22 carbomethoxyl functions in an anhydride ring closure reaction, was indicated by the presence of weak infrared absorption at 1780 cm^{-1} in the crude product. The absence of the less intense high frequency component of the anhydride doublet (ca. 1850 cm^{-1}) is probably due to the small amount of anhydride formed during the reaction.

This interpretation was supported first by the observation that the impurity responsible for this infrared band could be easily removed by filtering the product through neutral alumina and secondly by the room temperature transformation of the cis trimethyl ester 34 to methyl maleopimarate (28b) with boron trifluoride-etherate. A similar conversion of the bicyclo (2.2.2) octanedione 79 to the anhydride 80 with boron trifluoride-etherate in ethane dithiol has also been reported¹⁰⁶.

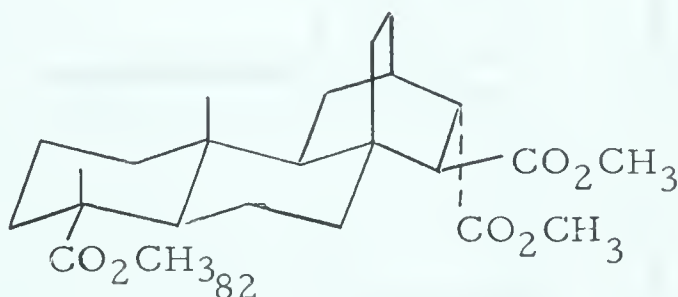


Refluxing the crude vinyl sulfide with sodium methoxide in methanol provided the oily trans vinyl sulfide 81, $\text{C}_{26}\text{H}_{38}\text{O}_6\text{S}$ as a colorless oil homogeneous to t.l.c. analysis after filtration through a short column of alumina.



The vinyl sulfide group was again identified by n.m.r. signals at 8.67, 8.56 and 4.70 τ and by ultraviolet absorption at 228 m μ ($\epsilon=8,840$ ¹⁴⁰). Epimerization of the C-21 ester group was established by a downfield shift of the C-21 and C-22 carbomethoxyl signals from 6.48 and 6.46 τ to 6.42 and 6.32 τ in the trans epimer 81 (spectra obtained in carbon tetrachloride solution, see page 182a for the n.m.r. spectrum of compound 81).

Desulfurization with W-2 Raney nickel in absolute ethanol provided the saturated trans trimethyl ester 82, C₂₄H₃₆O₆, m.p. 104-05°C in 90% yield.



The three ester groups were identified by infrared absorption at 1720 cm⁻¹ and by n.m.r. signals at 6.32, 6.34 and 6.35 τ . A trans arrangement of the C-21 and C-22 carbomethoxyl groups was indicated by the absence of carbonyl absorption at ca. 1745 cm⁻¹ and by the absence

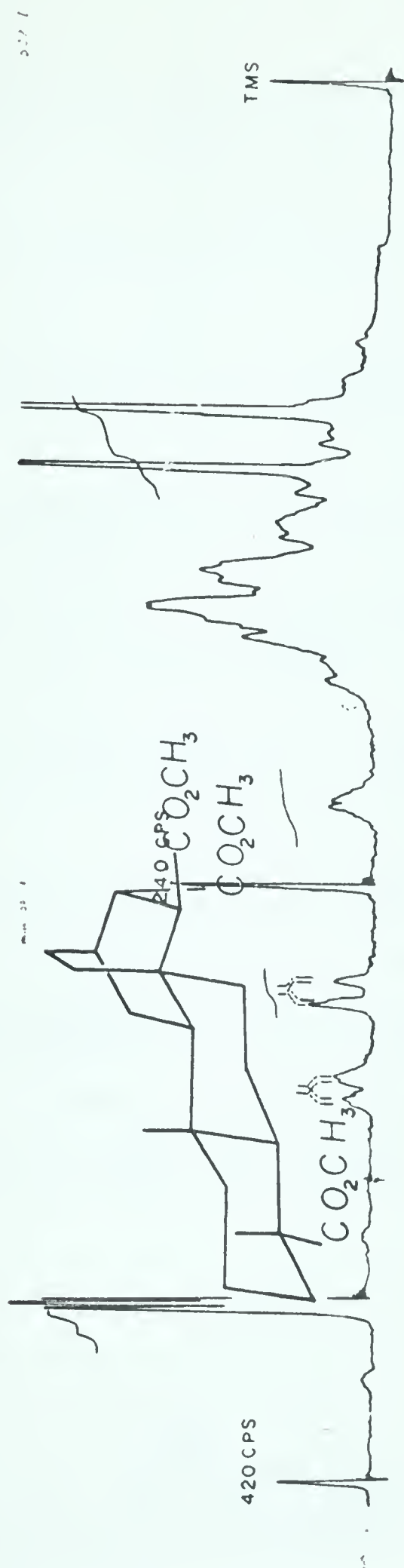


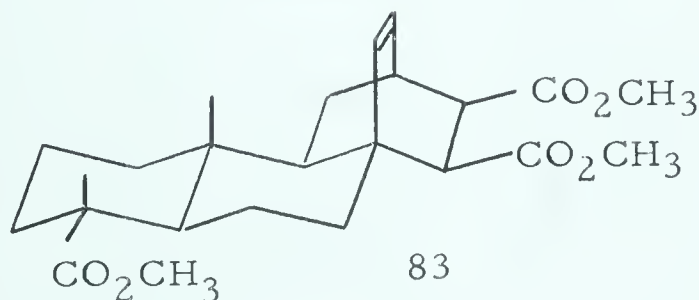
Figure 33. Nuclear magnetic resonance spectrum of the saturated trans trimethyl ester 82.
at 100 mc.

of a mutual shielding of these two functions as indicated by the relatively low field positions of the carbomethoxyl signals.

The proton attached to C-21 was represented by a pair of triplets centered at 6.98τ . With the aid of double irradiation experiments it was possible to show that two of the couplings involved the adjacent C-6 ($J = 2.2$ c.p.s.) and C-22 protons ($J = 6.7$ c.p.s.). A third coupling of 1.0 c.p.s. with a proton at 8.69τ is probably the result of a long range coupling with the C-5 β proton since this provides the sterically favourable 'W' arrangement^{76,77}.

The C-22 protons appeared as a pair of doublets at 7.29τ resulting from coupling with the C-21 proton and a small ($J = 1.3$ c.p.s.) long range coupling with a proton at 8.34τ presumably the C-8 exo proton for the reason referred to in the preceeding paragraphs.

Desulfurization of the crude vinyl sulfide 77, without prior treatment with sodium methoxide, using freshly prepared W-2 Raney nickel in boiling ethanol provided the olefin 83, $C_{24}H_{34}O_6$, m.p. $170-71^\circ C$ in 70% yield.



The n.m.r. data including the results of spin decoupling experiments are presented in Table IV.

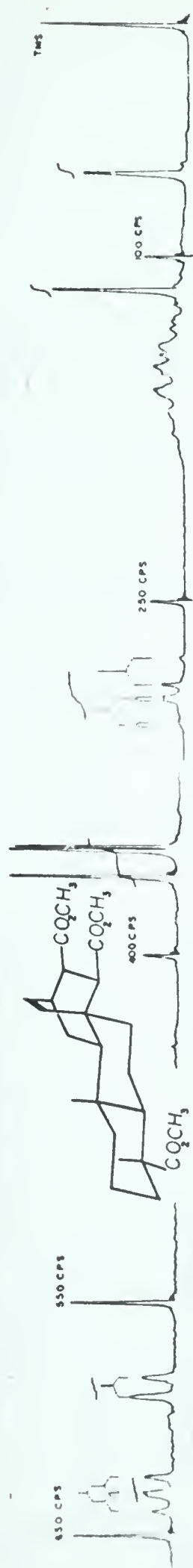
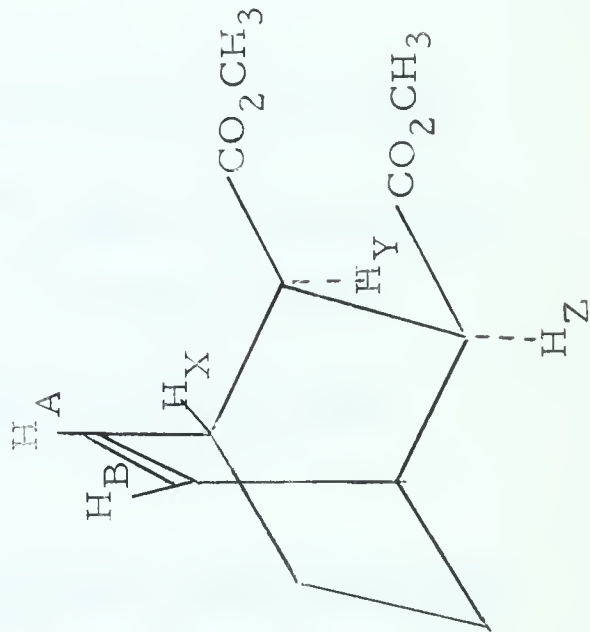


Figure 34. Nuclear magnetic resonance spectrum of the unsaturated cis trimethyl ester 83. at 100 mc.

TABLE IV

CHEMICAL SHIFTS AND COUPLING CONSTANTS ASSOCIATED WITH THE
CIS TRIMETHYL ESTER 83.

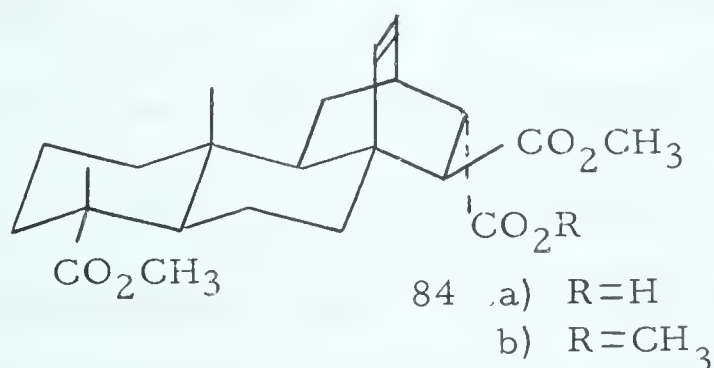
Proton	H _A	H _B	H _X	H _Y	H _Z	C-17	C-15 CO ₂ CH ₃	C-21 CO ₂ CH ₃	C-22 CO ₂ CH ₃
γ-value	3.68	4.14	7.10	7.08	7.17	9.36	6.33	6.44	6.45
Multiplicity	quartet	doublet		quartet	doublet				
J-values (c.p.s.)	J _{AB} =8.3 J _{AX} =6.8	J _{AB} =8.3		J _{XY} =2 J _{YZ} =11					



The appearance of the C-17 methyl signal at 9.36τ , which with one exception (the hydroxymethyl diester 36) is actually at somewhat lower field than observed in endocyclic olefins containing the C-7 isopropyl substituent, argues against a deshielding effect by this group as a rationalization of the diamagnetic shift exhibited by the C-17 protons in the methyl ketones 38, 56a, 56b and 64. The explanation therefore appears to lie in an increased shielding capacity of the $\alpha\beta$ unsaturated keto function relative to the isolated endocyclic double bond.

An endo and eclipsed arrangement of the C-21 and C-22 carbo-methoxyl groups in 83 was established by the shielded nature of the methoxyl hydrogens, by the characteristic coupling ($J = 11$ c.p.s.) between the hydrogens on carbons 21 and 22 and by a high frequency infrared band at 1742 cm^{-1} .

Mild saponification of the olefin 83 with dilute sodium hydroxide in aqueous methanol provided the monoacid 84a, m.p. $209-12^\circ\text{C}$.



The carboxyl group was identified by broad infrared absorption between 2400 and 3400 cm^{-1} and the two ester groups by carbomethoxyl signals at 6.38 and 6.32τ in the n.m.r. spectrum.

The argument for a C-21 exo carboxyl function is based on the analogous saponification of the cis trimethyl ester 34 and methyl ketone 38 to the corresponding monoacids 41 and 56b respectively, and is supported by the close similarity which the carbomethoxyl chemical shift values bear to those of the monoacids 41 and 56b (6.37, 6.30 τ and 6.37, 6.31 τ).

Esterification of the monoacid 84a with ethereal diazomethane provided the oily trimethyl ester 84b. A trans arrangement of the C-21 and C-22 carbomethoxyl groups was confirmed by a single low frequency carbonyl band at 1725 cm^{-1} in the infrared spectrum of the trimethyl ester and by carbomethoxyl signals at 6.40, 6.33 and 6.29 τ (cf. the trans esters 32, 56b, 58b, 58c, Table IV, page 176).

Analysis of the 7 τ region of the n.m.r. spectrum with the aid of spin decoupling experiments enabled identification of the C-6 proton as a broad multiplet centered at 7.10 τ underlying the C-22 doublet at 7.14 τ ($J = 5.8$ c.p.s.). The C-21 proton appeared as a pair of closely spaced triplets at 7.41 τ with spacings representing couplings of ca. 5.8, 2.5 and 2.5 c.p.s.. This coupling pattern is similar to that shown by the C-21 β proton of the saturated triester 82 and the keto trans trimethyl ester 60 and therefore argues for a similar steric arrangement in the unsaturated ester 84b. In particular, the large coupling (5.8 c.p.s.) is of the order expected for trans C-21 and C-22 protons. One of the smaller couplings was shown to involve the bridgehead methine while the second presumably involves a long range coupling with the C-5 α hydrogen

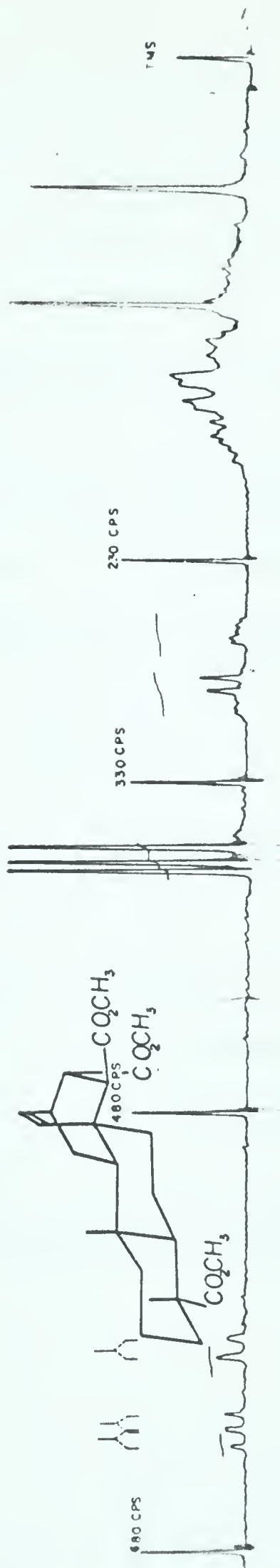
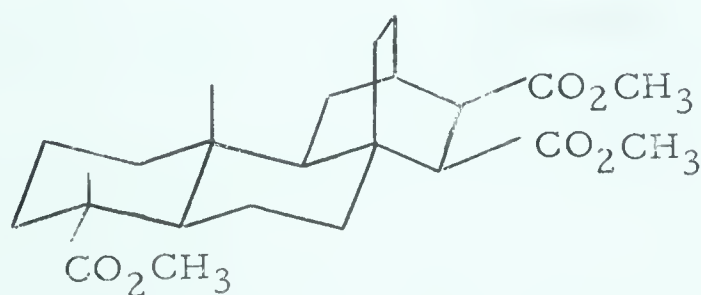


Figure 35. Nuclear magnetic resonance spectrum of the unsaturated trans trimethyl ester 64b.
at 100 mc.

similar to that encountered in the saturated analogs 82 and 60.

The clean doublet which characterizes the C-22 proton is in distinct contrast to its appearance as a pair of doublets in the saturated ester 82 and supports the postulation that the long range coupling causing this further splitting probably involves the exo proton of the C-8 methylene group since in the unsaturated ester 84b the vinyl hydrogen at C-8 does not provide the sterically favorable 'W' configuration.

The double bond of the unsaturated ester 84b was readily hydrogenated with W-2 Raney nickel in boiling ethanol and the product shown to be the saturated trimethyl ester 82 by melting point and infrared comparison with authentic material. In contrast to this facile reduction, the C-21 endo epimer (compound 83) showed a marked resistance towards hydrogenation, unchanged starting material being recovered both after attempted hydrogenation with platinum and hydrogen at elevated pressure (600-1100 p.s.i.) as well as from attempted chemical reduction using diimide generated in situ by the thermal decomposition of sulfonylhydrazine in refluxing diglyme¹⁰⁷. The saturated cis trimethyl ester 85 was eventually prepared, although still in a somewhat impure state, by the following procedure.



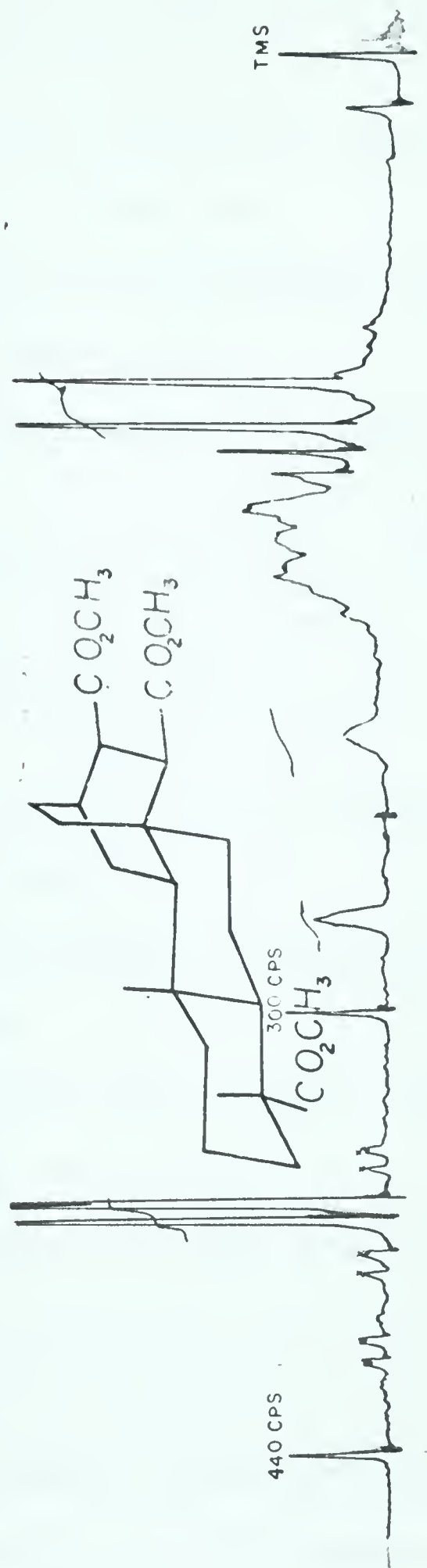


Figure 36. Nuclear magnetic resonance spectrum of the saturated cis trimethyl ester 85.
at 100 mc.

The keto trimethyl ester 59 was reacted for 30 minutes with a ten-fold excess of ethanedithiol in boron trifluoride-etherate and the impure thioketal, which was obtained as a colorless foam, desulfurized with W-2 Raney nickel in boiling ethanol. Chromatographic separation of the cis trimethyl ester 85 was complicated by the presence of a lactone, m.p. 207°, $\nu_{\max}$ 1765 cm^{-1} and 1718 cm^{-1} , possessing an almost identical Rf value. As a result considerable losses were incurred and the low yields of each component prevented complete characterizations.

Recrystallization of the saturated ester fraction provided the purified preparation, m.p. 128-31°C. The eclipsed C-21 and C-22 carbomethoxyl groups were identified by infrared absorption at 1745 cm^{-1} and by n.m.r. signals at 6.41 and 6.40 τ while the C-15 ester function appeared as a three proton peak at 6.34 τ . The presence of ethoxyl containing contaminants was indicated by a partially obscured triplet at 8.75 τ ($J=7.2$ c.p.s.) and a pair of quartets at 5.92 and 5.94 τ ($J=7.2$ c.p.s.) and confirmed by appropriate spin decoupling experiments. Although attempted ester exchange with methanol-HCl was unsuccessful it is nonetheless felt that the impurities are ethyl esters since the chemical shift values of the methylene protons are in the expected range (5.90 τ)¹⁰⁸.

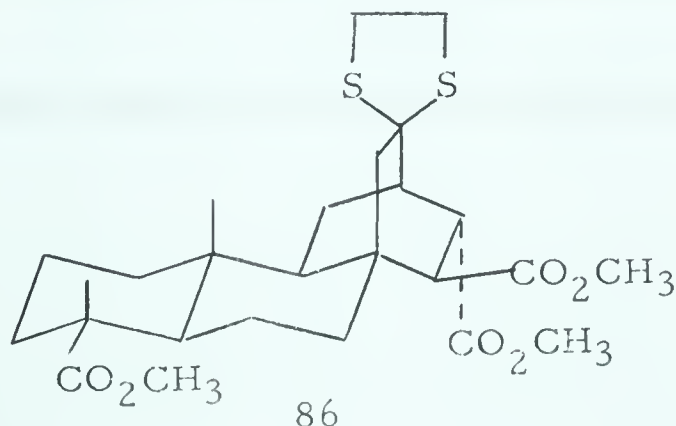
Epimerization of the saturated cis trimethyl ester 85 with sodium methoxide in anhydrous methanol provided the trans ester 82 identified by melting point, mixture melting point and infrared spectral comparisons.

The crude thioketal resulting from the addition of ethanedithiol

to the bicyclic ketone 59 could be purified by first filtering the crude product through a short column of alumina to remove the anhydride impurity and then refluxing it with sodium methoxide in methanol-tetrahydrofuran to remove the thiolic ester groups.

The oily 1,3 dithiolane 86 which was homogeneous to two dimensional t.l.c. analysis, showed the expected 4 proton signal at 6.77τ due to the thioketal function and C-methyl peaks at 8.88 and 8.91 τ representing the C-16 and C-17 methyl groups respectively. The paramagnetic shift (ca. 0.1 p.p.m.) of the C-17 protons relative to their normal value is similar to that observed in the hydroxy triester 61 and may arise from an analogous deshielding effect of the sulfur atom.

The ester groups were identified by infrared absorption at 1722 cm^{-1} and carbomethoxyl signals at 6.38, 6.36 and 6.30 τ (spectra obtained in CCl_4 solution). The presence of a C-21 exo substituent was indicated by the absence of carbonyl absorption at 1745 cm^{-1} and shielded carbomethoxyl signals, and was confirmed by desulfurization with W-2 Raney nickel in ethanol to the saturated trimethyl ester 82 identified by melting point and infrared spectral comparison.



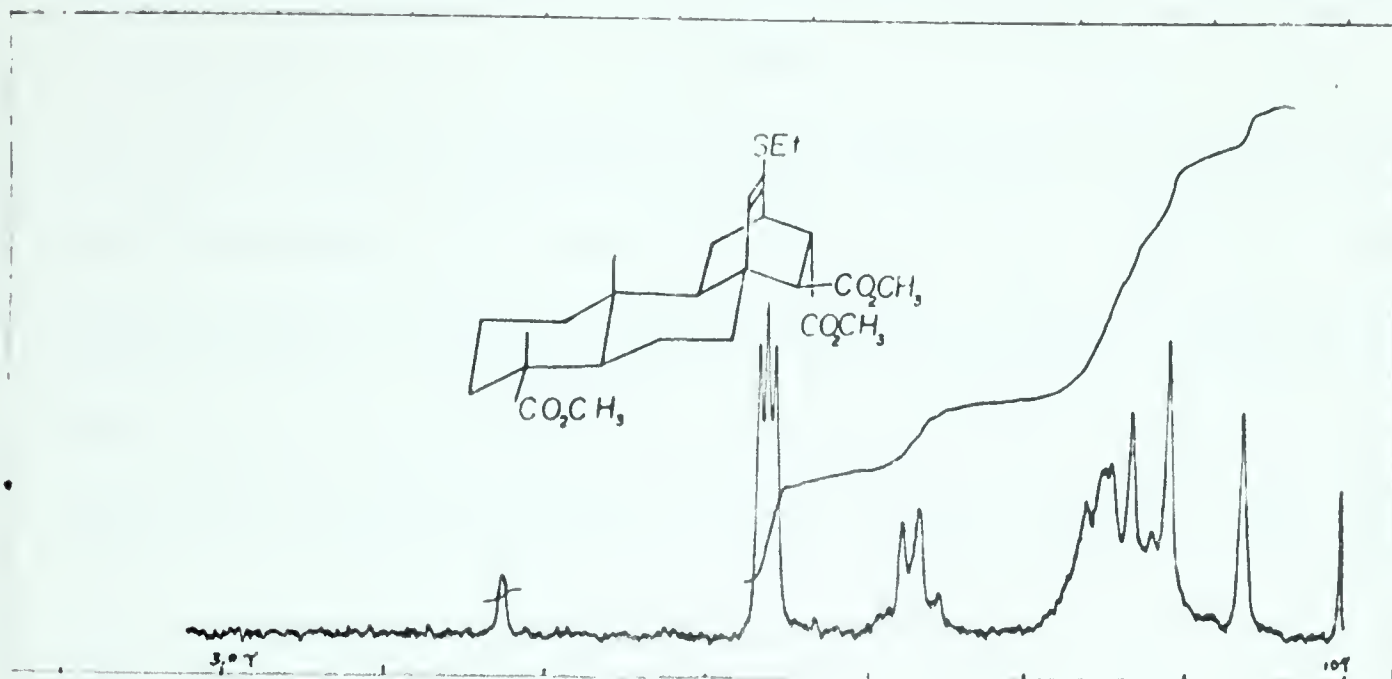


Figure 66. Nuclear magnetic resonance spectrum of the vinyl sulfide 81.

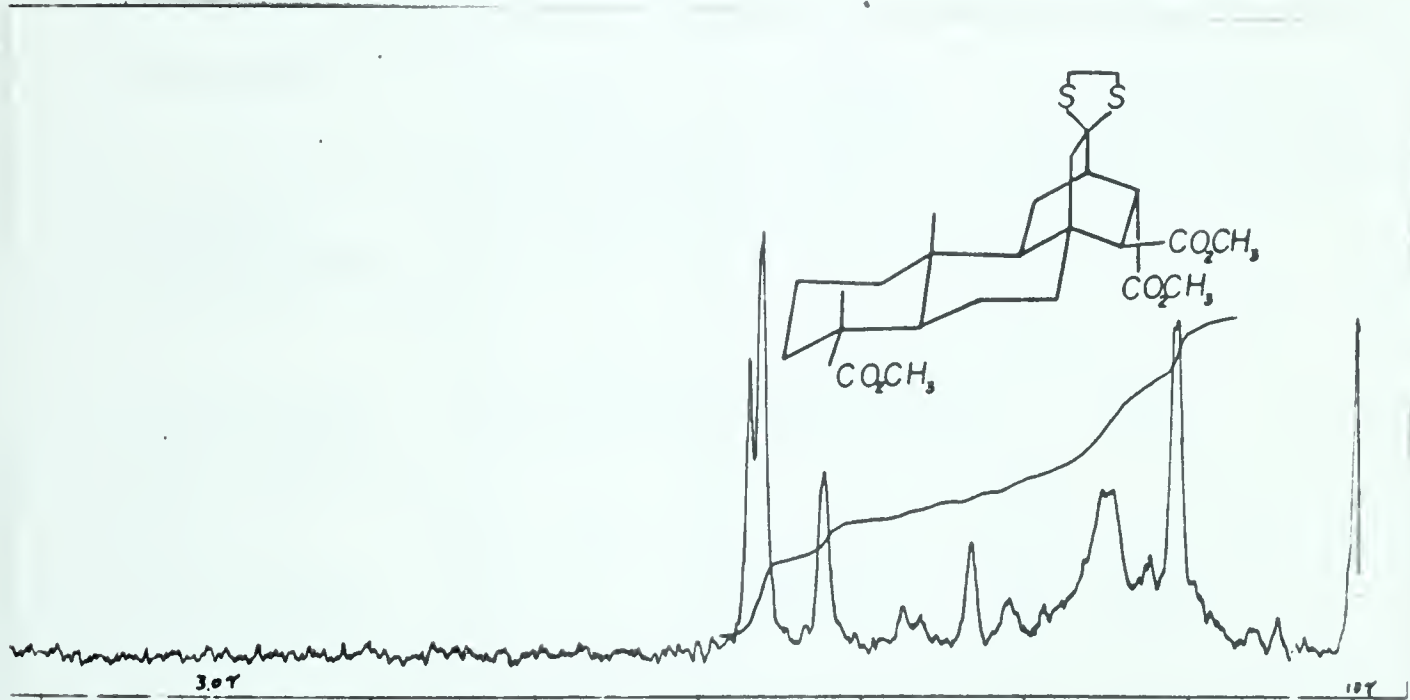


Figure 67. Nuclear magnetic resonance spectrum of the thioketal 86.

Evaluation of Shielding Effects on the C-21 and C-22 Carbomethoxyl Groups.

In the following n.m.r. analysis the earlier measurement of the carbomethoxyl shielding parameter ($\Delta\sigma_C$, equation (1) page 169) is confirmed, a direct measurement of the olefinic shielding contribution ($\Delta\sigma_O$) is made, and evidence is obtained for a deshielding effect of the double bond on an exo C-21 carbomethoxyl group. The important n.m.r. signals are summarized in Table V.

TABLE V
SHIELDING EFFECTS ASSOCIATED WITH C-21 AND C-22 CARBO-
METHOXYL GROUPS.

Compound	C-21 CO ₂ CH ₃	C-22 CO ₂ CH ₃	Relative Configuration	C-15 CO ₂ CH ₃
Saturated cis trimethyl ester 85	6.40 (6.41)	6.41 (6.40)	cis	6.34
Unsaturated cis trimethyl ester 83	6.44 (6.45)	6.45 (6.44)	cis	6.33
Unsaturated monoacid 84a	--	6.39	trans	6.33
Unsaturated trimethyl ester 84b	6.29	6.40	trans	6.33
Saturated trans trimethyl ester 82	6.32	6.35	trans	6.34

From the data listed Table V for compounds 83, 84a and 84b the shielding constant $\Delta\delta_C$ for a C-22 carbomethoxyl group is readily assigned a value of 0.05 ± 0.01 p.p.m. somewhat lower than the previous value of 0.07 ± 0.02 p.p.m.. Comparison of the chemical shift values for the saturated and unsaturated cis trimethyl esters 85 and 83 as well as for the saturated and unsaturated trans trimethyl esters 82 and 84b provide the first direct measurement of $\Delta\delta_O$ (0.04 and 0.05 p.p.m. respectively) the shielding contribution of the olefinic bond on an endo carbomethoxyl group. The calculation of $\Delta\delta_X$, a collection of miscellaneous deshielding effects which accompany epimerization of the C-21 carbomethoxyl group to an exo orientation can now be made if it is assumed as before, that the measurement of $\Delta\delta_C$ is also valid for the C-21 ester group.

$$\Delta\delta_T = \Delta\delta_C + \Delta\delta_O + \Delta\delta_X$$

(1) Saturated cis trimethyl ester 85 $\rightarrow$ trans trimethyl ester 82

$$0.12 - 0.13 = 0.05 \pm 0.01 + 0.04 + \Delta\delta_X$$

$$\Delta\delta_X = 0.02 - 0.05 \text{ p.p.m.}$$

(2) Unsaturated cis trimethyl ester 83 $\rightarrow$ unsaturated trans ester 84b

$$0.15 - 0.16 = 0.05 \pm 0.01 + 0.04 + \Delta\delta_X$$

$$\Delta\delta_X = 0.05 - 0.08 \text{ p.p.m.}$$

From these calculations it would appear that removal of the double bond can cause the exo C-21 carbomethoxyl protons to shift upfield by 0.03 p.p.m., thereby accounting for a sizeable portion of the $\Delta\delta_X$ term. This diamagnetic shift is not entirely surprising since the C-21

exo carbomethoxyl group lies in the deshielding cone of the double bond.

A similar pattern is also found in the isopropylidene trimethyl ester 45 and the ketone 60 both of which contain C-21 exo carbomethoxyl signals at 6.27 τ that shift upfield to 6.33 and 6.32 τ in the saturated analogs 44b and 82. Presumably the methoxyl protons are being deshielded by the isopropylidene double bond and the C-7 carbonyl group.

In conclusion, these results are taken as indication that the double bond between carbons 7 and 8 in the various maleopimaric acid derivatives shields the angular methyl at C-12 by ca. 0.35 p.p.m. and endo C-21 or C-22 carbomethoxyl groups by 0.04-0.05 p.p.m.. In addition, the data suggests that the double bond may exert a small deshielding effect on a C-21 exo carbomethoxyl group (0.03 p.p.m.). Finally, the paramagnetic shift of the C-22 carbomethoxyl signal (0.07 ± 0.02 p.p.m.) which accompanies epimerization at C-21 suggests the presence of a mutual shielding effect by the eclipsed carbomethoxyl groups.

EXPERIMENTAL

a) Preparation of the saturated trans trimethyl ester 82

The bicyclic ketone (1.01 g., 2.4 mmoles) was dissolved in 9.33 g. of ethyl mercaptan, 6 mls of boron trifluoride-etherate added and the solution allowed to stand at room temperature for 15 minutes. It was then diluted with benzene, washed twice with 2% aqueous sodium hydroxide then several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The oily product, chiefly the vinyl sulfide 77 possessed the following spectral characteristics. Infrared spectrum: $\checkmark_{\max}$ 1780(s)(anhydride), 1745(sh), 1727(s), 1685(w). Nuclear magnetic resonance spectrum (CCl_4): γ 9.34(3H), 8.88(3H), 8.68(t, $J=7$ cps), 7.0-7.5(6H), 6.48(3H), 6.46(3H), 6.36(3H), 4.63(1H). Thin layer chromatographic analysis (alumina plates, KMnO_4 spray) established the presence of a second minor component in the reaction product. Trituration with ether provided 50 mgs of crystalline precipitate (compound 78), melting point $207-209^\circ\text{C}$, after several recrystallizations from ethyl acetate. Calc. for $\text{C}_{25}\text{H}_{36}\text{O}_6\text{S}$: C, 64.62; H, 7.81; S, 6.90%. Found: C, 64.75; H, 7.67; S, 6.05%. Infrared spectrum: $\checkmark_{\max}^{\text{CHCl}_3}$ 1715-1740(s), 1670(m), 1405 cm^{-1} (m). Nuclear magnetic resonance spectrum (CDCl_3); γ 9.18(3H), 8.86(3H), 6.8-7.5($\sim$ 7H), 6.42 and 6.38(shoulders), 6.36 and 6.32(8-9H). Ultraviolet spectrum: $\lambda_{\max}$ 238m μ ($\epsilon = 2400$).

0.5 g. of the non-crystalline portion of the product was refluxed for 1.5 hours in 70 mls of anhydrous methanol containing 25 mmoles of sodium methoxide. The solvent was then removed under vacuum, dilute aqueous HCl added to the residue and the organic precipitate taken up in several chloroform washes. The combined chloroform solution was

washed with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. A portion of the oily residue (0.3 g.) was chromatographed on 5 g. of neutral alumina, the Skellysolve forerun (150 mls) being discarded. Elution with 300 mls of 1:1 Skellysolve-ether provided 200 mgs of the vinyl sulfide 81 as a colourless oil homogeneous to t.l.c. analysis. The analytical sample was prepared by vacuum distilling this oil at 150°C. Calc. for $C_{26}H_{38}O_6S$: C, 65.25; H, 8.00; S, 6.69%. Found: C, 65.27; H, 8.11; S, 6.53%. Infrared spectrum: $\nu_{\max}$ 1725 $cm^{-1}(s)$. Nuclear magnetic resonance spectrum (CCl_4); τ 9.37(3H), 8.90(3H), 8.67, 7.1-7.5($\sim$ 5H), 6.42(3H), 6.37(3H), 6.32(3H), 4.70(1H). Ultraviolet absorption: $\lambda_{\max}$ 228(ϵ = 8840).

125 mgs (0.26 mmoles) of the oily vinyl sulfide were refluxed for 18 hours in 20 mls of absolute ethanol containing ca 0.5 g. of W-2 Raney nickel. The solution was then filtered through a sintered glass funnel, the nickel washed with methanol and the filtrate concentrated. Benzene was added to the semi-solid residue, an amorphous solid removed by filtration and the filtrate again concentrated. The oily residue (98 mgs, 90% yield) crystallized on triturating with methanol. Recrystallization from Skellysolve B and methanol provided the pure trans trimethyl ester 82, melting point 104-5°C. Calc. for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63; O, 22.83%. Found: C, 68.33; H, 8.45; O, 23.31%. Infrared spectrum: $\nu_{\max}$ 1720 $cm^{-1}(s)$. Nuclear magnetic resonance spectrum: τ 9.01(3H), 8.84(3H), 7.85(1H, broad), 7.29(1H, 2d, $J_1=6.7$ cps, $J_2=1.3$ cps), 6.98(1H, 2t, $J_1=6.7$ cps, $J_2=2.2$ cps, $J_3=1.0$ cps), 6.35(3H), 6.34(3H), 6.32(3H). R.D. curve in methanol ($c = 0.214$), plain negative dispersion curve. $[\alpha]_{700}^{-56^\circ}$ $[\alpha]_D^{-56^\circ}$ $[\alpha]_{500}^{-64^\circ}$ $[\alpha]_{400}^{-103^\circ}$ $[\alpha]_{300}^{-318^\circ}$ $[\alpha]_{250}^{-1,000^\circ}$

b) Preparation of the unsaturated cis trimethyl ester 83.

The bicyclic ketone 59 (0.740 g., 1.70 mmoles) was allowed to react with 10 mls of 40% ethanethiol in boron trifluoride-etherate for 15 minutes. The reaction mixture was then transferred to a separatory funnel, diluted with benzene (60 mls), washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The colourless oil was dissolved in 50 mls of 95% ethanol and refluxed for 6 hours with 4 g. of freshly prepared W-2 Raney nickel (a preliminary attempt to desulfurize the vinyl sulfide by refluxing in ethanol for 11 hours with deactivated W-2 Raney nickel did not measurably decrease the ultraviolet absorption at 228 μ). The solution was then filtered, the nickel washed with ethanol and the filtrate evaporated. Ethyl acetate was added to the solid residue, the solution filtered free of a small amount of insoluble material and evaporated. The crystalline residue (.50 g., m.p. 140-65°C), after recrystallizing from methanol and benzene-Skellysolve B provided the analytically pure olefin 83, melting point 170-71°C. Calc. for C₂₄H₃₄O₆: C, 68.87; H, 8.20; O, 22.94%. Found: C, 69.07; H, 8.15; O, 23.41%. Infrared spectrum: $\sqrt{\text{max}}$ 1742(s), 1722 cm⁻¹(s). Nuclear magnetic resonance spectrum: γ 9.36(3H), 8.86(3H), 7.21(1H, J=11 cps), 7.05(1H, 2d, J₁=11 cps, J₂=1.3 cps), 6.45(3H), 6.44(3H), 6.33(3H), 4.14(1H, d, J=8.3 cps), 3.68(1H, J₁=8.3, J₂=6.8 cps). R.D. in methanol (c = 0.265): $[\alpha]_{700}^{-56^{\circ}}$ $[\alpha]_{D}^{-65^{\circ}}$ $[\alpha]_{500}^{-81^{\circ}}$ $[\alpha]_{400}^{-121^{\circ}}$ $[\alpha]_{350}^{-154^{\circ}}$ $[\alpha]_{300}^{-201^{\circ}}$ $[\alpha]_{270}^{-216^{\circ}}$

Attempted hydrogenation of the unsaturated trimethyl ester 83

i. Catalytic

62 mgs of the cis trimethyl ester was dissolved in 25 mls of

methanol containing 50 mgs of platinum oxide and hydrogenated for 42 hours. During this period the hydrogen pressure dropped from 1100 psi to 600 psi. The catalyst was then removed by filtration and the filtrate concentrated. Two recrystallizations of the solid residue from methanol provided the unsaturated ester 83, melting point 168-70°C, identified by its infrared and n.m.r. spectra.

ii. Chemical

A solution of 40 mgs (0.096 mmoles) of the unsaturated trimethyl ester in 50 mls of diglyme (distilled from LiAlH_4) was heated to the reflux temperature and 82 mgs (0.48 mmoles) of sulfonylhydrazine in 25 mls of diglyme added dropwise over a 40 minute period. Refluxing was continued under a nitrogen blanket for 1.5 hours, the solution then cooled, diluted with water and the organic precipitate dissolved in benzene. The benzene solution was extracted several times with 10% aqueous potassium carbonate, washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization of the solid residue gave needles, melting point 170-71°C, shown to be unchanged starting material by m.m.p. and infrared comparison with the unsaturated trimethyl ester 83.

c) Preparation of the unsaturated trans trimethyl ester 84b.

The unsaturated cis trimethyl ester (0.42 g., 1.0 mmoles) was refluxed for 30 minutes in 35 mls of a 0.6 molar solution of sodium hydroxide in 30% aqueous methanol. The reaction mixture was then diluted with aqueous HCl and extracted four times with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization from ethyl acetate and then benzene-

Skellysolve B provided the pure monoacid 84a, melting point 209-212°C.

Infrared spectrum: $\checkmark_{\max}^{\text{CHCl}_3}$ 3400-2400(broad), 1690-1710 cm^{-1} (s).

Nuclear magnetic resonance spectrum: τ 9.38(3H), 8.86(3H), 6.8-7.5(3H), 6.39(3H), 6.33(3H), 4.13(1H, d, $J=8$ cps), 3.73(1H, $J_1=8$ cps, $J_2=6.5$ cps).

Esterification of the monoacid 84a with ethereal diazomethane followed by evaporation of the solvent provided the oily trans trimethyl ester 84b. Infrared spectrum: $\checkmark_{\max}$ 1725(s). Nuclear magnetic resonance spectrum: τ 9.40(3H), 8.87(3H), 7.41(1H, sextet), 7.14(1H, d, $J=5.8$ cps), 7.10(1H, broad quartet), 6.40(3H), 6.33(3H), 6.29(3H), 4.13(1H, d, $J=8.5$ cps), 3.76(1H, quartet, $J_1=8.5$ cps, $J_2=6.5$ cps).

R.D. in methanol: ($c = 0.22$): plain positive dispersion curve,

$[\alpha]_{700}^{-4^\circ}$ $[\alpha]_{\text{D}}^{-2^\circ}$ $[\alpha]_{450}^{+2^\circ}$ $[\alpha]_{400}^{+11^\circ}$ $[\alpha]_{350}^{+29^\circ}$ $[\alpha]_{300}^{+61^\circ}$ $[\alpha]_{275}^{+95^\circ}$
 $[\alpha]_{250}^{+152^\circ}$

- d) Conversion of the unsaturated trans trimethyl ester 84b to the saturated trans trimethyl ester 82.

The trimethyl ester 84b obtained by esterifying 58 mgs of the monoacid 84a with diazomethane, was dissolved in 20 mls of 95% ethanol and refluxed for 8 hours with 2 g. of W-2 Raney nickel. The nickel was then filtered off and the filtrate evaporated. Two recrystallizations from methanol provided 23 mgs of needles, melting point 104-105°C, the infrared spectrum of which was identical with that of the trans trimethyl ester 82.

- e) Conversion of the bicyclic ketone 59 to the saturated trans trimethyl ester 82 via the thioketal derivative 86.

The bicyclic ketone 59 (0.145 g., 0.334 mmoles) was allowed to

stand in a solution of 0.30 g. (3.2 mmoles) of ethanedithiol and 0.6 mls of redistilled boron trifluoride etherate for 30 minutes. Water was then added and the organic precipitate collected in several ether washes. These were combined and extracted first with distilled water, then dilute sodium hydroxide and finally distilled water. The solution was then dried over anhydrous magnesium sulfate, filtered, and evaporated. The impure thioketal (166 mgs), which was obtained as a colourless foam, possessed the following spectral properties. Infrared spectrum:

$\checkmark_{\max}$ 1770(w), (anhydride), 1730(sh), 1720 cm^{-1} (s). Nuclear magnetic resonance spectrum (CCl_4): τ 8.89(6H), 6.6-7.6($\sim$ 11H), 6.40, 6.38($\checkmark$ 6H).

The thioketal was separated from the anhydride contaminant by filtration through 5 g. of neutral alumina (elution with benzene and benzene-ether (3:1) and then refluxed for 5.5 hours in 15 mls of 1:1 methanol-T.H.F. containing 3.9 mmoles of sodium methoxide. Following this the solvent was evaporated, dilute aqueous HCl added and the organic precipitate collected by two benzene extractions. These were combined, washed with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. The oily residue was treated with ethereal diazomethane and the solvent again removed. The thioketal 86, obtained as a colourless oil, was homogenous to two dimensional t.l.c. analysis. Infrared spectrum: $\checkmark_{\max}$ 1722 cm^{-1} (s). Nuclear magnetic resonance spectrum (CCl_4): τ 8.91(3H), 8.88(3H), 7.2-7.8(3H), 6.77(4H), 6.38(3H), 6.36(3H), 6.30(3H).

A portion of the thioketal 86 (1.8 g.) was refluxed for 16 hours in 75 mls of anhydrous methanol containing 1 g. of W-2 Raney nickel. Evaporation of the solvent, addition of benzene and removal of an insoluble amorphous solid by filtration provided 0.8 g. of oily

residue which from n.m.r. analysis still contained ca. 60% unchanged starting material. The residue was therefore refluxed an additional 19 hours in 75 mls of absolute ethanol containing 0.5 g. of W-2 Raney nickel. The oily desulfurized product (0.30 g.), isolated in the usual manner, was chromatographed on neutral alumina. A forerun of 1:1 benzene-Skellysolve B (150 mls) provided a small amount of oil which was not investigated further. Elution with benzene (0.20 l) yielded the trans trimethyl ester 82, melting point 104-105°C after recrystallization from Skellysolve B. The infrared spectrum was identical with that of the sample obtained by desulfurizing the vinyl sulfide 81. Elution with 1:10 ether-benzene provided several oily fractions followed by a second crystalline component, melting point 150-151°C, shown to be the keto trans trimethyl ester 60 by comparison of its infrared spectrum with that of authentic material.

f) Preparation of the saturated cis trimethyl ester 85

The bicyclic ketone 59 was converted to the thioketal as described in the previous experiment and the crude product, without prior treatment with sodium methoxide, refluxed in 60 mls of ethanol (distilled from calcium oxide) containing 4 g. of W-2 Raney nickel for 11 hours. The nickel was then removed by filtration, washed with 100 mls of ethanol and the filtrate evaporated. Benzene was added to the residue, the solution filtered free of an amorphous solid, evaporated and the residual opaque oil subjected to the following purification procedure.

Chromatography on neutral alumina (5 g., chromatography #1) provided, on elution with benzene (150 mls, fractions 1-3), 42 mgs of the impure saturated cis trimethyl ester 85, melting point 118-124°C after

two recrystallizations from Skellysolve B. The sample was further purified by recrystallization from methanol and Skellysolve (m.p. 128-131°C). Infrared spectrum: $\checkmark_{\max}$ 1745(s), 1724 cm^{-1} (s). Nuclear magnetic resonance spectrum: $\checkmark$ 8.97(3H), 8.83($\checkmark$ 4H), 8.75(t, J=7.2 cps), 7.86(2H, broad), 7.29(2H), 6.41 and 6.40(4.5-5.0H), 6.34(3H), 5.94 and 5.92($\checkmark$ 1H, quartets, J=7.2). R.D. in methanol (c = 0.202), plain negative dispersion curve: $\left[\alpha\right]_{700}^{-45^{\circ}}$ $\left[\alpha\right]_{600}^{-47^{\circ}}$ $\left[\alpha\right]_{500}^{-61^{\circ}}$ $\left[\alpha\right]_{400}^{-83^{\circ}}$ $\left[\alpha\right]_{300}^{-188^{\circ}}$ $\left[\alpha\right]_{250}^{-495^{\circ}}$.

Continued elution with benzene (250 mls, fractions 4-7 and 3% ether in benzene (150 mls, fractions ⁸⁻¹⁰8-10) yielded a mixture of the trimethyl ester 85 and a lactonic compound ($\checkmark_{\max}$ 1765(s), 1718 cm^{-1} (s)). These were partially separated by combining fractions 4-10 (wt. 50 mgs) and rechromatographing on 5 g. of neutral alumina (chromatography #2). Elution with benzene (100 mls), 3% ether in benzene (100 mls), and 6% ether in benzene (100 mls) provided only a negligible amount of material. Fractions 4-5 (100 mls of 10% ether in benzene) yielded a small amount of the impure trimethyl ester 85, melting point 120-121°C after three recrystallizations from Skellysolve B. The lactonic compound, melting point 207°C was obtained from fractions 6 and 7 (100 mls of 10% ether in benzene) and purified by recrystallizing from Skellysolve B. A more complete characterization of this compound was not carried out due to a lack of material.

The final fractions of chromatography #1 (11-15, 300 mls of 3% ether in benzene, and 16-18, 150 mls of 6% ether in benzene) appeared to contain a third compound. Thus, when fractions 11-18 were combined, sublimed under vacuum at 150°C and recrystallized from Skellysolve B, a small amount of crystalline material, melting point 143-153°C was obtained.

The infrared spectrum (semi-micro cell) showed absorption at 1722 cm^{-1} and a fingerprint region ($1400\text{--}1000\text{ cm}^{-1}$) which, within the limits of resolution, was identical with the trimethyl ester 85. Further investigation, however, as in the case of the lactone, was made impossible by the very small amount of material available.

- g) Treatment of the trimethyl ester 85 with methanolic HCl - attempted ester exchange.

The trimethyl ester 85 (ca. 50 mgs) was refluxed for 1.5 hours in 14 mls of anhydrous methanol containing 1.0 g. of anhydrous HCl. The solution was then evaporated, water added and the aqueous solution extracted twice with benzene. The combined benzene extracts were then washed twice with water, dried over anhydrous magnesium sulfate, filtered and evaporated. Two recrystallizations from methanol provided 36 mgs of the trimethyl ester 85, m.p. $121\text{--}123^{\circ}\text{C}$ still containing the ethyl group (n.m.r. signals at 8.78τ , 6.07τ and 5.96τ ($\sim 1\text{H}$)). The trimethyl ester was therefore redissolved in methanolic HCl and allowed to stand for six days at room temperature. Isolation of the trimethyl ester was effected in the manner described above. Successive recrystallizations from benzene and Skellysolve provided the n.m.r. sample, m.p. $120\text{--}124^{\circ}\text{C}$. The spectrum showed ethoxyl absorption at 8.76 , 6.00 and 5.88τ .

- h) Epimerization of the saturated cis trimethyl ester 85.

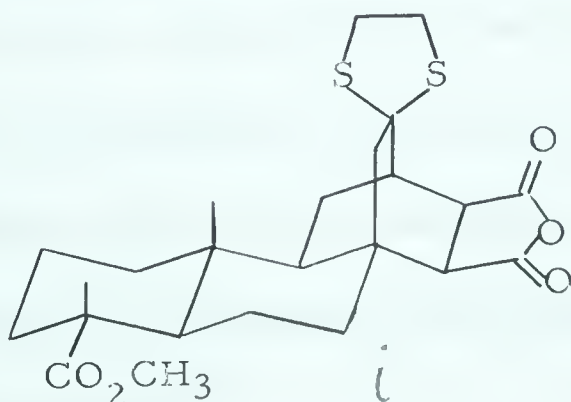
The trimethyl ester recovered from the unsuccessful ester exchange experiments described in the preceding section was allowed to react at room temperature over a $3\frac{1}{2}$ day period with 3.8 mmoles of sodium methoxide in 5 mls of anhydrous methanol. The reaction mixture was then diluted with water and extracted several times with chloroform. The

combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and evaporated. Three recrystallizations from methanol provided 7 mgs of needles, melting point 101-103°C, the infrared spectrum (CCl_4 solution) of which was identical with that of the trans trimethyl ester 82. The melting point of the purified sample (105-106°C) was not depressed on admixture with authentic trimethyl ester 82.

j) Prolonged reaction of the keto trimethyl ester 59 with ethane dithiol in BF_3 -etherate.

The keto trimethyl ester 59 (0.57 g.) was allowed to stand in a solution of ethanedithiol (4 mls) and redistilled boron trifluoride-etherate (2 mls) for 4 days. The solution was then diluted with benzene, extracted with 2N sodium hydroxide, washed with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residual oil (200 mgs) possessed the following spectral properties. Infrared spectrum: ν_{max} 1850(m), 1770(s), 1720 cm^{-1} (s). Nuclear magnetic resonance spectrum (CCl_4): τ 8.86(6H), 7.18(3H), 6.67(4H), 6.37(3H).

Several recrystallizations from benzene-Skellysolve B and ethyl acetate provided the purified anhydride i, melting point 239-242°C. Calc. for $\text{C}_{22}\text{H}_{28}\text{S}_2\text{O}_5$: C, 62.03; H, 6.95; S, 13.80%. Found: C, 61.79; H, 7.13; S, 13.80%.

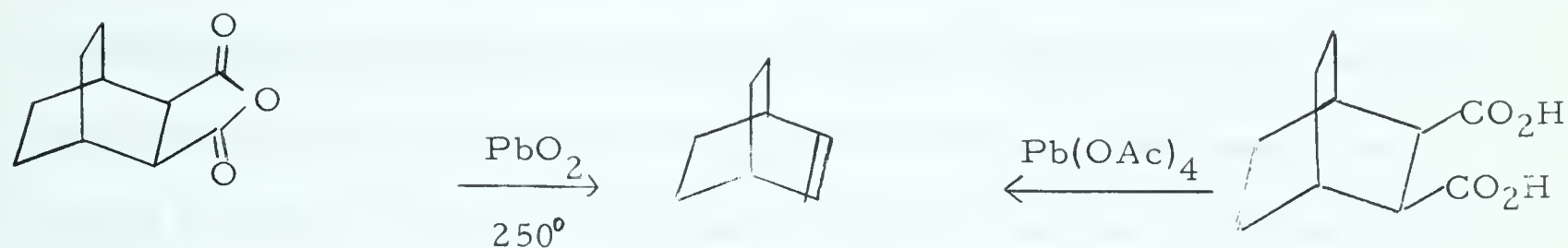


3. OXIDATIVE BISDECARBOXYLATION OF METHYL FUMAROPIMARATE (42) WITH LEAD TETRAACETATE.

A. INTRODUCTION

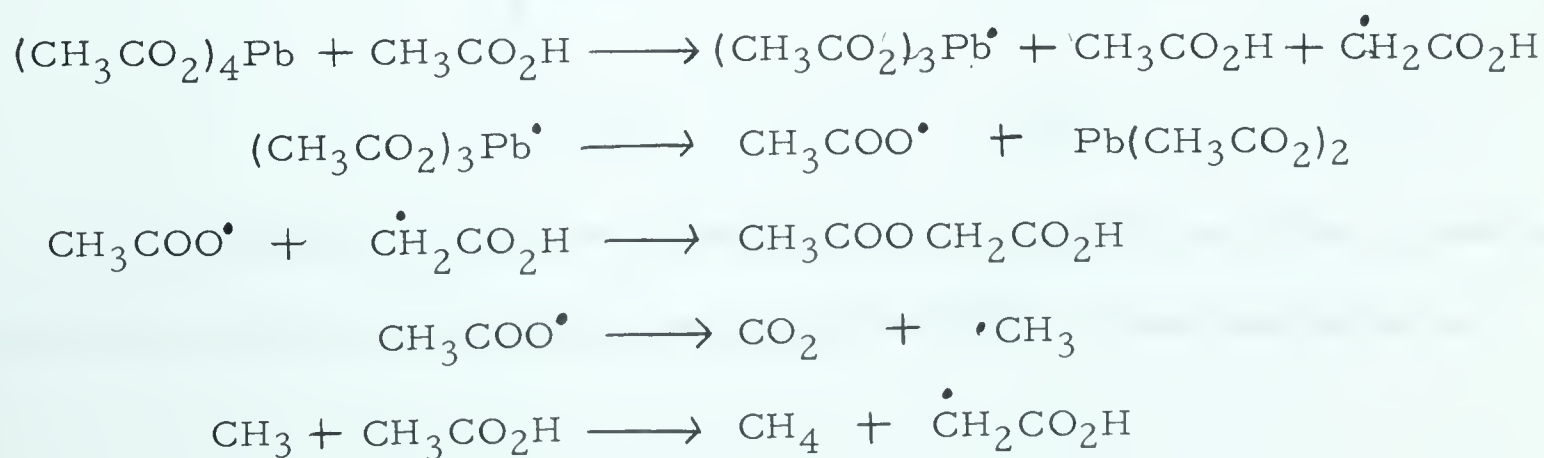
The reaction between methyl fumaropimarate and lead tetraacetate was first investigated because of the need to develop a method for removing the C-21 and C-22 carboxyl groups of maleopimaric acid in the attempt to correlate atisine with the resin acids through the tetracyclic degradation product 25. In this connection, the reported ability of lead tetraacetate to decarboxylate 1,2-dicarboxylic acids¹¹⁶ seemed to provide a simple answer to this difficulty in working with a maleic anhydride Diels-Alder adduct since no difficulty was anticipated in hydrogenating the olefin expected from this reaction.

The lead tetraacetate oxidation, which is an outgrowth of a similar bisdecarboxylation with lead dioxide first reported by von Doering and co-workers in 1952¹¹⁷, possesses the advantage that it permits the use of organic solvents and lower reaction temperatures than required with lead dioxide. The yields, probably because of these milder conditions are invariably higher. For example, bisdecarboxylation of bicyclo (2.2.2) octane-2,3-dicarboxylic anhydride with lead dioxide required a reaction temperature of 250° and provided bicyclo (2.2.2) octene in a rather mediocre 20% yield¹¹⁷ whereas with lead tetraacetate oxidative bisdecarboxylation of the corresponding 1,2 dicarboxylic acid gave bicyclo (2.2.2) octene in approximately 60% yield¹¹⁸.

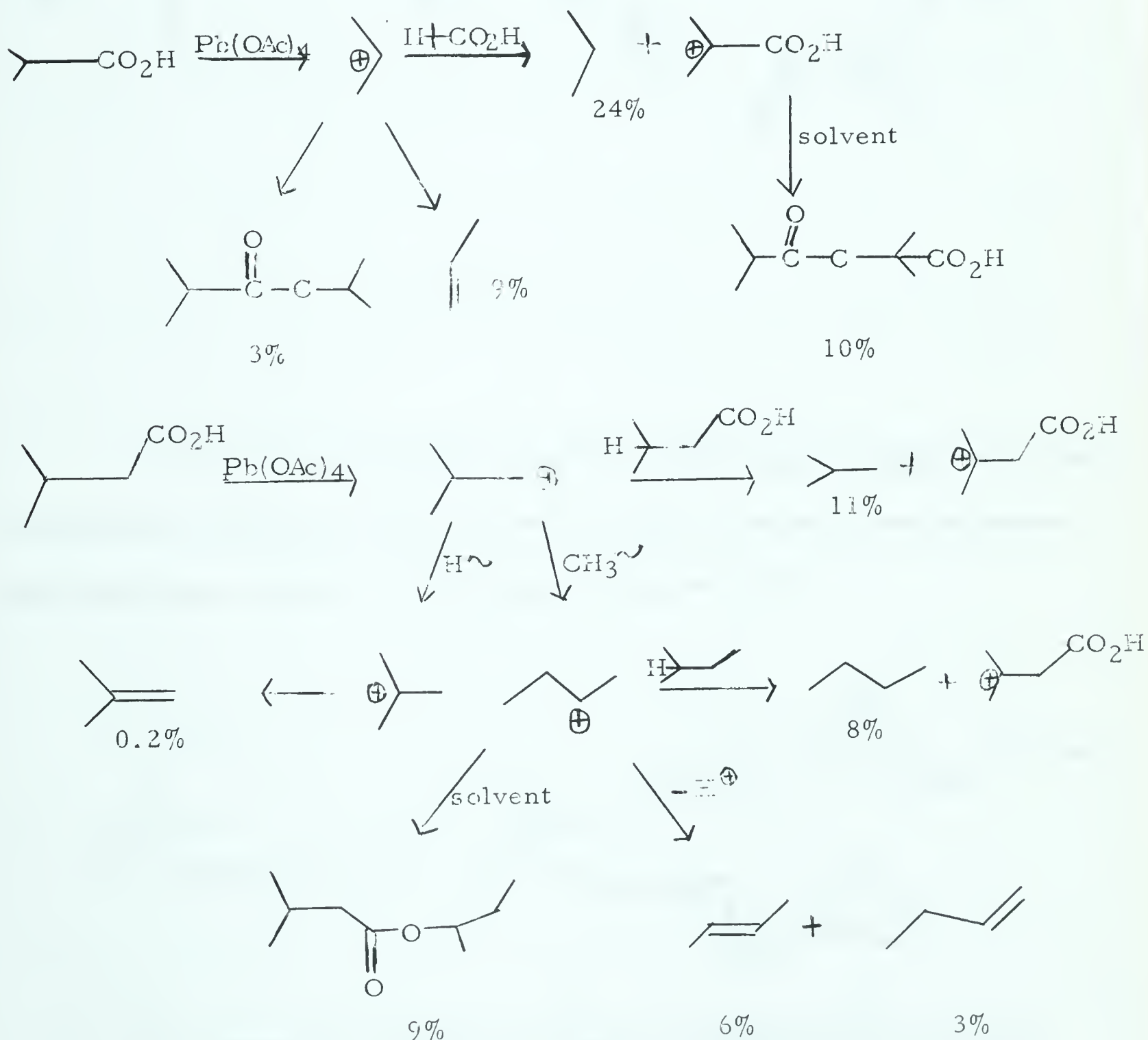


The question of whether or not these decarboxylations involve a cyclic intermediate of the type postulated¹¹⁹ in the lead tetraacetate cleavage of some α glycols has been studied by E. J. Corey and J. Casanova¹²⁰. These workers have found that the lead tetraacetate decarboxylation of both meso and d,l - 1,2 diphenyl succinic acids gave the same product - trans stilbene and on the basis of this observation have suggested that a labile monocarboxylic intermediate rather than a cyclic intermediate is probably involved. Further information on the nature of these transient species has been obtained from the results of investigations on monocarboxylic acids.

The earliest of these studies is that by Kharash and co-workers on the decomposition of lead tetraacetate in boiling acetic acid¹²¹. The major products of this reaction have been found to be CO_2 (0.42 moles), methane (0.3 moles) and acetoxy acetic acid (0.4 moles) and their formation has been rationalized in terms of the following radical mechanism.

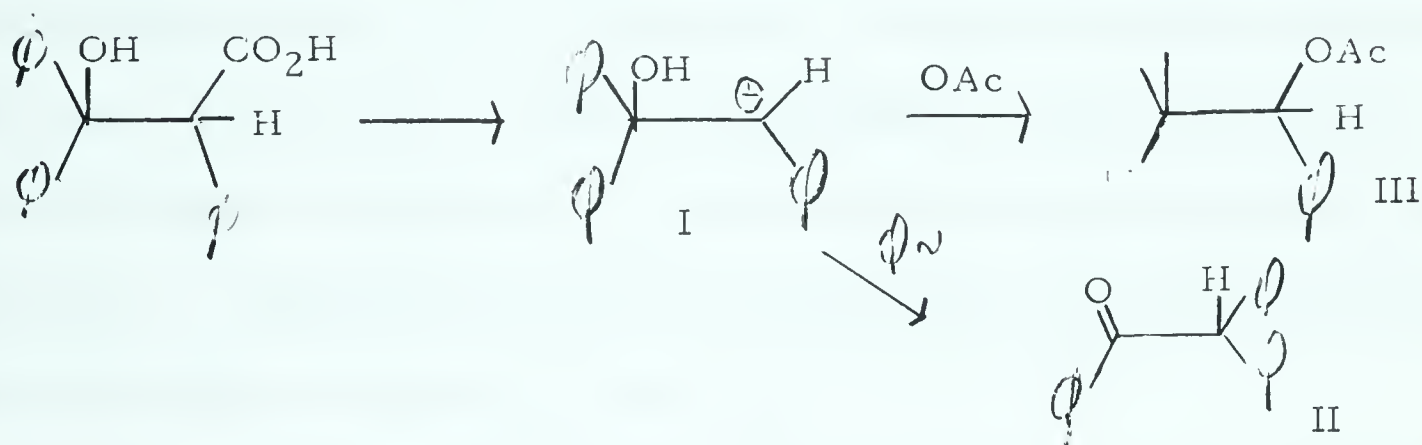


In a later investigation W. A. Mosher and C. L. Kehr have examined the decomposition of triphenyl acetic, trimethyl acetic, isobutyric and isovaleric acids with lead tetraacetate¹²² and have interpreted their results in terms of ionic intermediates primarily because of the carbonium type rearrangement observed with isovaleric and isobutyric acids (see below).

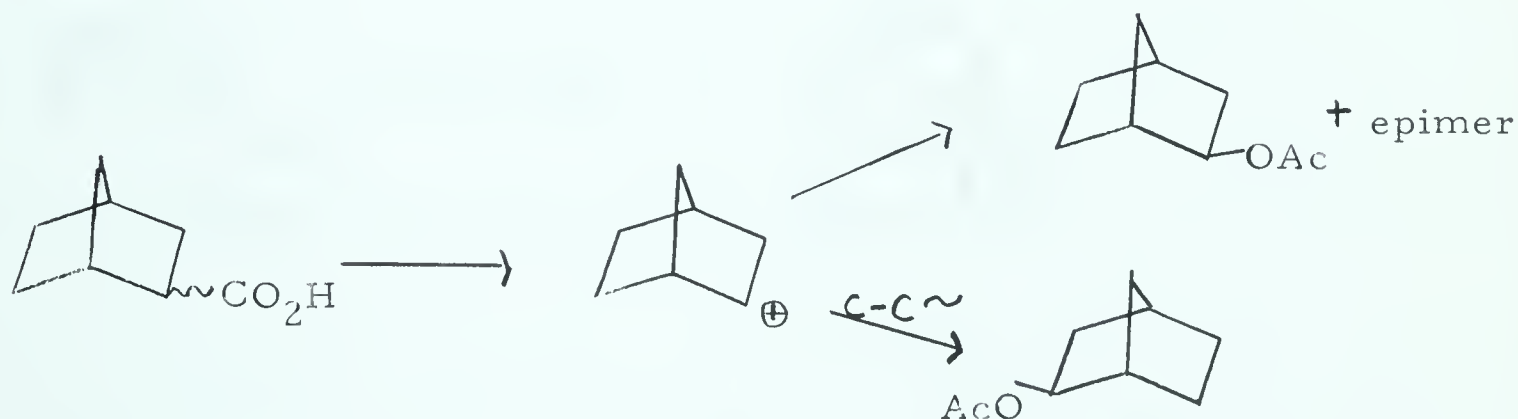


Recently, Corey and Casanova have reported two other systems for which cationic intermediates are postulated¹²⁰. Decarboxylation of

$\alpha\beta\beta$ triphenyl- β -hydroxypropionic acid with lead tetraacetate in benzene provided the rearranged ketone II and the unrearranged acetate III both of which are expected of the intermediate I.



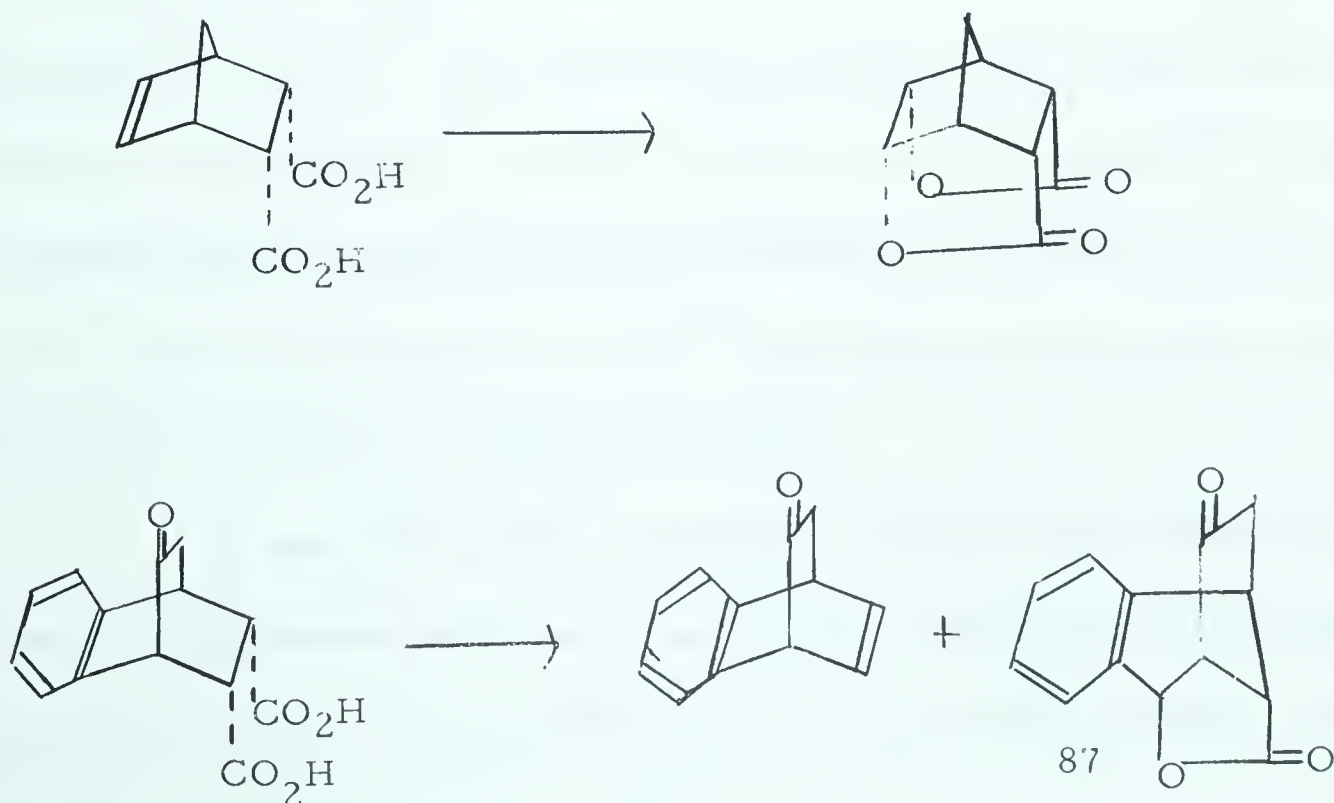
In the decarboxylation of optically active exo and endo norbornane-2 carboxylic acids these workers have encountered skeletal rearrangement which they argue involves the classical carbonium ion IV.



In summary, therefore, it can be concluded that the reaction of lead tetraacetate with both monocarboxylic and dicarboxylic acids probably involves an initial ester exchange forming the mixed ester

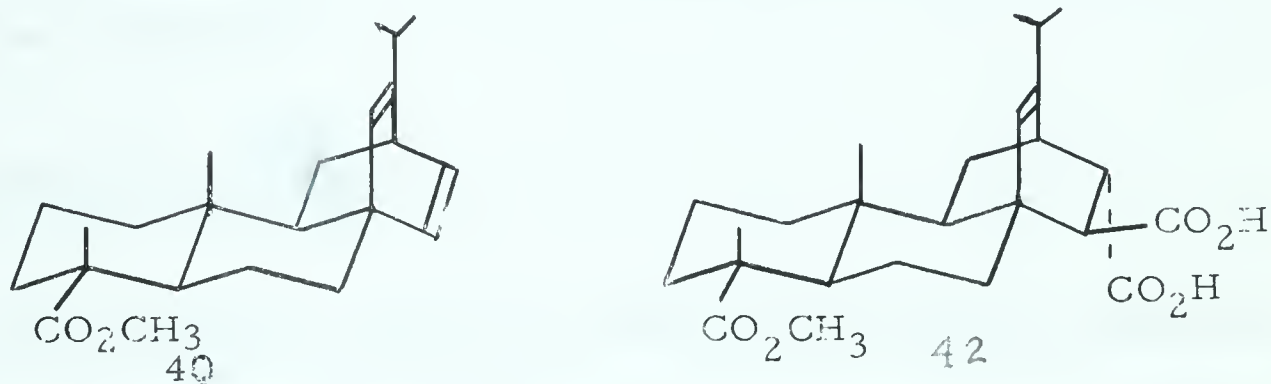
$R-O-Pb(OAc)_3^{123}$ which then undergoes a homolytic decarboxylation followed by (in the case of reactions which involve a carbonium ion) a fast electron transfer from radical to $Pb(OAc)_3$. In cases where the carbonium ion is unfavored (e.g., the decomposition of lead tetraacetate itself) this last step does not occur. These intermediates are then converted to products either by expulsion of a proton leading to olefin formation or by saturation, generally through the incorporation of a solvent molecule, but occasionally by hydrogen abstraction.

Of special interest in connection with the present work because of the similarity which these compounds bear to methyl fumaropimarate is the dilactonization of bicyclo (2.2.1) heptene dicarboxylic acid¹²⁴ and the formation of a rearranged lactone 87 from benzobicyclo (2.2.2) octene dicarboxylic acid¹²⁵ on treatment with lead tetraacetate.



B. RESULTS AND DISCUSSION

The dicarboxylic acid used in these investigations, methyl fumaropimarate (42), was generally prepared by Diels-Alder addition of fumaric acid to impure methyl abietate although in some of the earlier experiments it was also obtained by either a partial saponification of the cis trimethyl ester 34 or by hydrolysis of the anhydride ring of methyl maleopimarate with sodium hydroxide in aqueous alcohol.



The decarboxylation of methyl fumaropimarate with lead tetraacetate, as mentioned earlier, was investigated because of the desire to develop a method for removing the C-21 and C-22 carboxyl groups of maleopimaric acid. The solvent used in the earlier experiments was pyridine which had been recently introduced by Grovenstein⁶⁰, while in some of the later studies which are discussed at the end of this section, use is also made of dimethylsulfoxide¹²³, tetrahydrofuran-acetic acid and acetic acid containing sodium acetate¹²⁶.

In one of the more thoroughly studied experiments a 1.4 molar excess of lead tetraacetate was reacted with methyl fumaropimarate in pyridine between 30°C and 45°C and the crude product divided into acidic

and neutral components. Chromatography of the neutral products on silica gel provided first the anticipated diene 40, $C_{23}H_{34}O_2$, as a colorless oil in ca. 10% yield, then a lactone, melting point 176-80°C, $C_{24}H_{34}O_4$, which will be referred to as lactone II and finally an acetoxy lactone (lactone I), melting point 194-95°C, $C_{26}H_{36}O_6$, in 7% and 3% yields respectively. Chromatography of the acidic components, also on silica gel, gave, in addition to some unchanged starting material, a third lactone (lactone III), melting point 189-90°C, $C_{25}H_{34}O_6 \cdot \frac{1}{2}C_6H_6$ (recrystallized from benzene) in 6% yield.

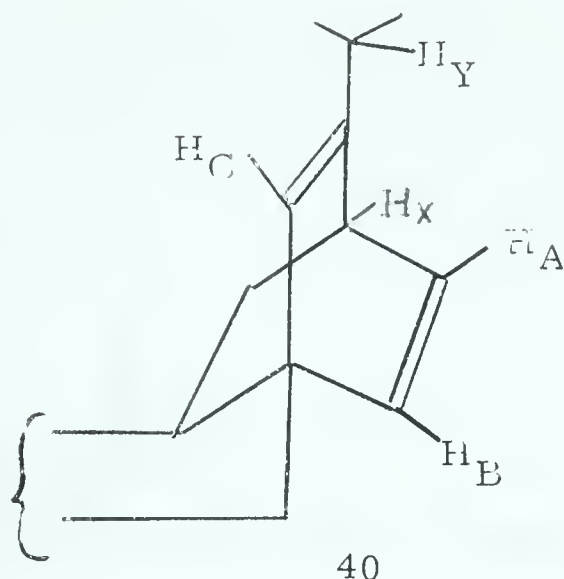
Structure Proof of the Diene 40.

The diene 40, $C_{23}H_{34}O_2$, molecular ion 342, was obtained as a colourless oil homogenous to two dimensional t.l.c. analysis, infrared absorption at 3040 cm^{-1} and 1732 cm^{-1} . The n.m.r. data is presented in Table VI. The assignments were verified by double irradiation experiments whenever possible.

TABLE VI

CHEMICAL SHIFTS AND COUPLING CONSTANTS ASSOCIATED WITH THE
DIENE 40

Proton	H_A	H_B	H_C	H_X	H_Y	C_1	C_{17}	C_{19}, C_{20}
$\mathcal{T}$ -value	3.84	4.05	4.59	6.75	7.70	8.88	9.38	8.98, 9.00
Multiplicity	quartet	quartet	triplet	multi- plet	multi- plet			2 doublets
J-values (c.p.s.)	$J_{AB}=7$ $J_{AX}=6$	$J_{BX}=1.5$	$J_{YC}=1.7$ $J_{XC}=\text{small}$					$J_{XC_{19}}=7$ $J_{XC_{20}}=7$



Evidence for the unrearranged bicyclo octadiene system in the diene is found in the magnitude of J_{AX} (6 c.p.s.) and J_{AB} (7 c.p.s.) which are in the range expected allylic and vinylic couplings in cyclohexene systems⁸⁷⁻⁹², and in the extent to which the C-12 angular methyl is shielded by the double bond. The small couplings observed between the protons H_XH_C , H_YH_C and H_XH_B are consistent with the allylic positions of H_X and H_Y . It is noteworthy that because of the rigidity of the bicyclo-octadiene system H_X cannot couple to H_C and H_B by the normal $\sigma \rightarrow \pi$ mechanism. Presumably in these cases a σ bond mechanism is operative since the intervening C-H and C-C bonds exist in the geometrically favorable 'W' arrangement⁷⁶.

The diene 40 was thermally unstable, undergoing a reverse Diels-Alder reaction to the extent of a ca. 75% in 30 minutes at 180°C. N.m.r. signals at 3.0-3.3 τ (2.5H) and 8.78 τ ($J=7$ c.p.s.) as well as u.v. maxima at 254, 262, 270 and 274 $m\mu$ are indicative of an aromatization process (structure 90) paralleling the thermal transformation of bicyclo (2.2.2) octa diene 88¹²⁷ and 'barrelene' 89 to benzene¹²⁸.



Figure 37. Nuclear magnetic resonance spectrum of the diene 40. at 100 mc.

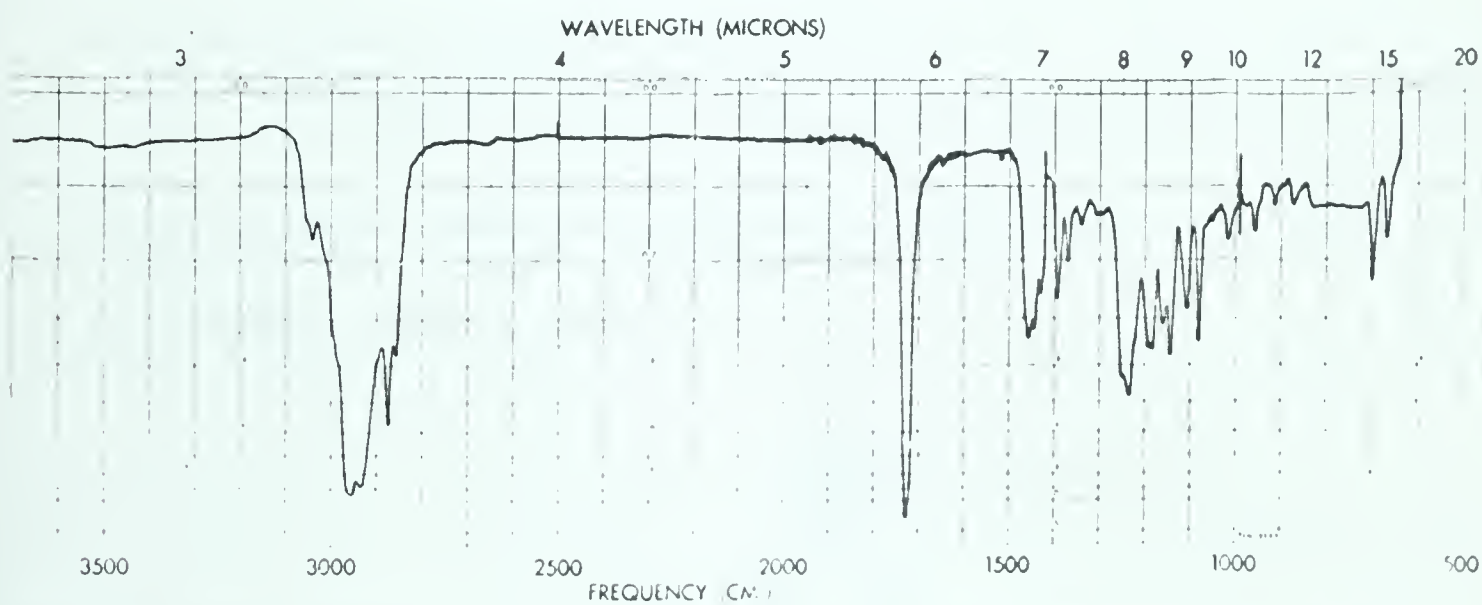
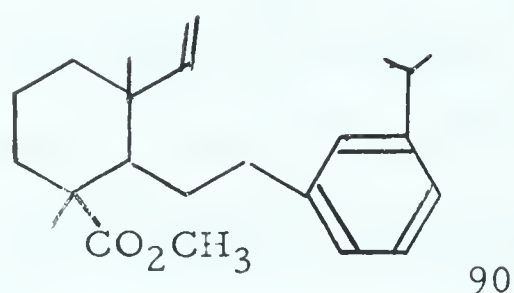
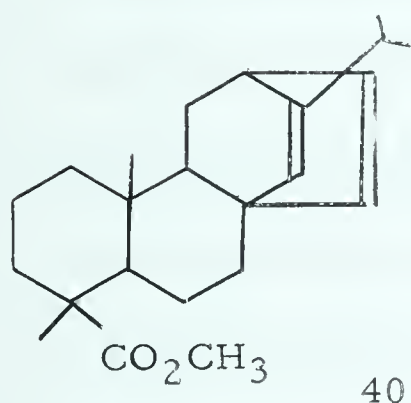
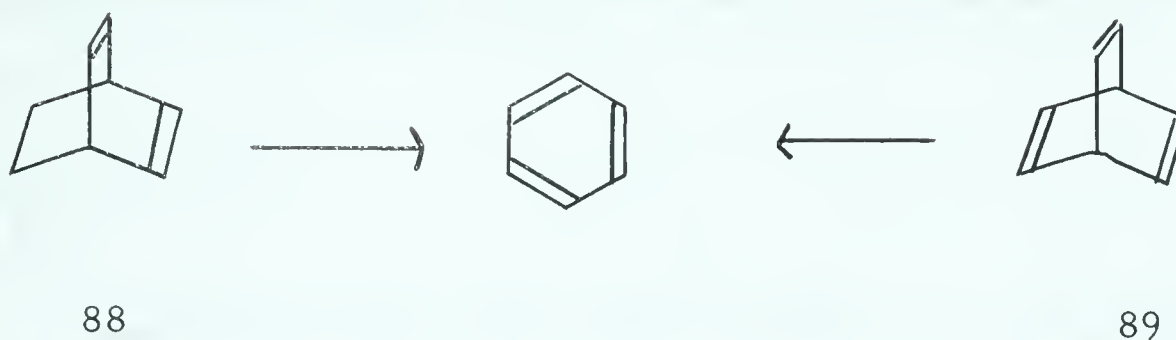
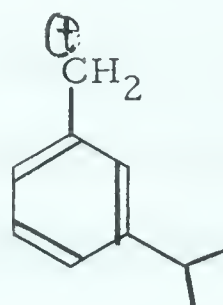


Figure 38. Infrared spectrum of the diene 40.



This interpretation is supported by the appearance in the mass spectrum of the base peak at $m/e = 133$. Formation of this peak can be rationalized in terms of the same type of retro Diels-Alder reaction proposed above followed by subsequent benzylic fragmentation leading to formation of the ion A



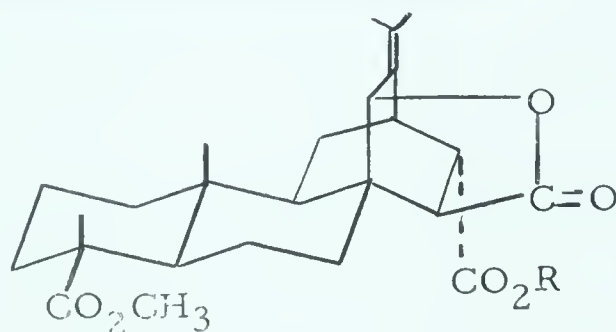
A $m/e = 133$

Hydrogenation of the diene 40 with platinum in methanol gave the oily dihydro derivative 91. As expected on steric grounds only the C-21, C-22 double bond was reduced as shown by the n.m.r. spectrum which contained a single one proton peak in the olefinic region at 4.60 τ

and a high field methyl signal at 9.42τ due to the shielded methyl group at C-12.

Lactone III

Lactone III, m.p. $189-90^{\circ}\text{C}$ analyzed for $\text{C}_{25}\text{H}_{34}\text{O}_6 \cdot \frac{1}{2}\text{C}_6\text{H}_6$ (recrystallization from benzene). The γ lactone was identified by a band in the infrared at 1771 cm^{-1} and in the n.m.r. spectrum by 1 proton signals at 4.97 ($\text{H}-\text{C}-\overset{\text{O}}{\parallel}\text{C}$) and 7.28τ ($\text{H}-\text{C}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{C}_8$). The carboxyl group was indicated by broad absorption in the $3200-2600\text{ cm}^{-1}$ region and by a sharp peak at 1710 cm^{-1} . The presence of a tetrasubstituted isopropylidene group in lactone III was established by a sharp six proton signal at 8.20τ and the absence of any signals which could be attributed to olefinic protons. Two peaks in the saturated C-methyl region at 8.84τ and 9.27τ were identified with the C-1 and C-12 methyl groups respectively, the latter group being shielded by the olefinic bond. Esterification of lactone III with diazomethane yielded the dimethyl ester $\text{C}_{25}\text{H}_{36}\text{O}_6$, m.p. $180-81^{\circ}\text{C}$, ν_{max} 1770 (s) , 1733 (s) , 1725 (s) . The appearance of a second carbomethoxyl signal in the n.m.r. spectrum confirmed the presence of a carboxyl group in lactone III and together with the above data leads to its formulation as structure 92.



- 92 a) $\text{R}=\text{H}$
 b) $\text{R}=\text{CH}_3$

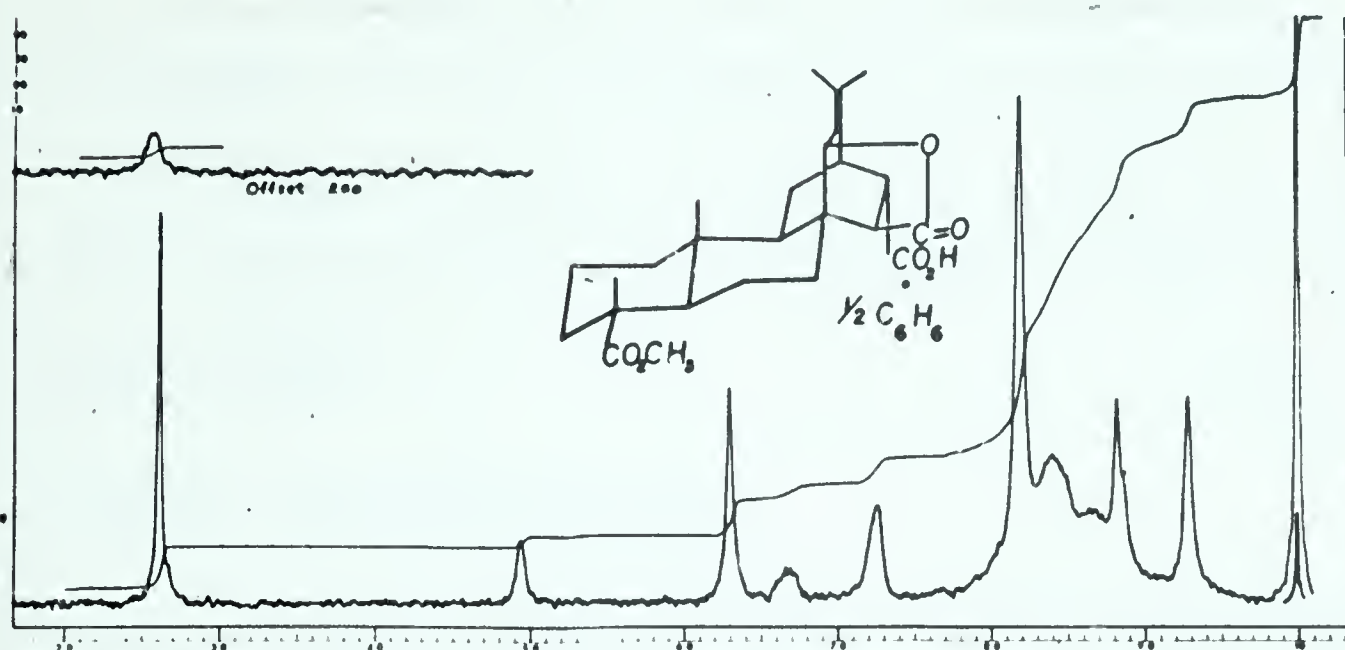


Figure 39. Nuclear magnetic resonance spectrum of lactone III.



Figure 40. Infrared spectrum of lactone III.

Formation of lactone III provides direct chemical support for a C-21 exo, C-22 endo arrangement of carboxyl groups previously assigned to methyl fumaropimarate (42) and to fumaropimaric acid (32a) on the basis of their formation under the equilibrating conditions of the Diels-Alder reaction.

Lactone I - Structure Elucidation

Lactone I analyzed for the molecular formula $C_{26}H_{36}O_6$ (mol. wt. 444) indicating the introduction of one unsaturation in its formation from the diacid 42. The molecular weight, determined by the Rast method, was 480, in reasonable agreement with the above figure and confirming the monomeric nature of lactone I.

The n.m.r. spectrum of lactone I showed the presence of four saturated C-methyl groups. Of these, two are sharp three proton signals at 8.79 and 9.05 τ assigned to the quarternary C-1 and C-12 methyls respectively. The remaining C-methyl signals are assigned to the isopropyl group and are characterized by an unusually high degree of non-equivalence, appearing as a pair of doublets at 8.94 τ ($J=7$ c.p.s.) and 9.16 τ ($J=7$ c. p.s.). Confirmation of this assignment is provided through a decoupling experiment in which the doublets were collapsed to a pair of singlets or irradiation at 8.12 τ .

The C-1 carbomethoxyl group as expected remained unchanged during the lead tetraacetate oxidation and is identified in the n.m.r. spectrum of lactone I by a three proton signal at $\tau=6.31$ and by a band in the infrared spectrum at 1722 cm^{-1} .

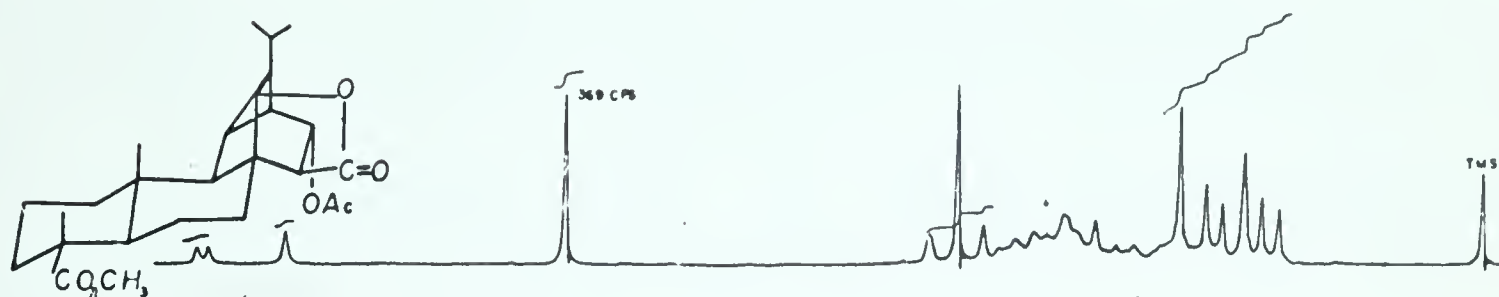


Figure 41. Nuclear magnetic resonance spectrum of lactone I.
at 100 mc.

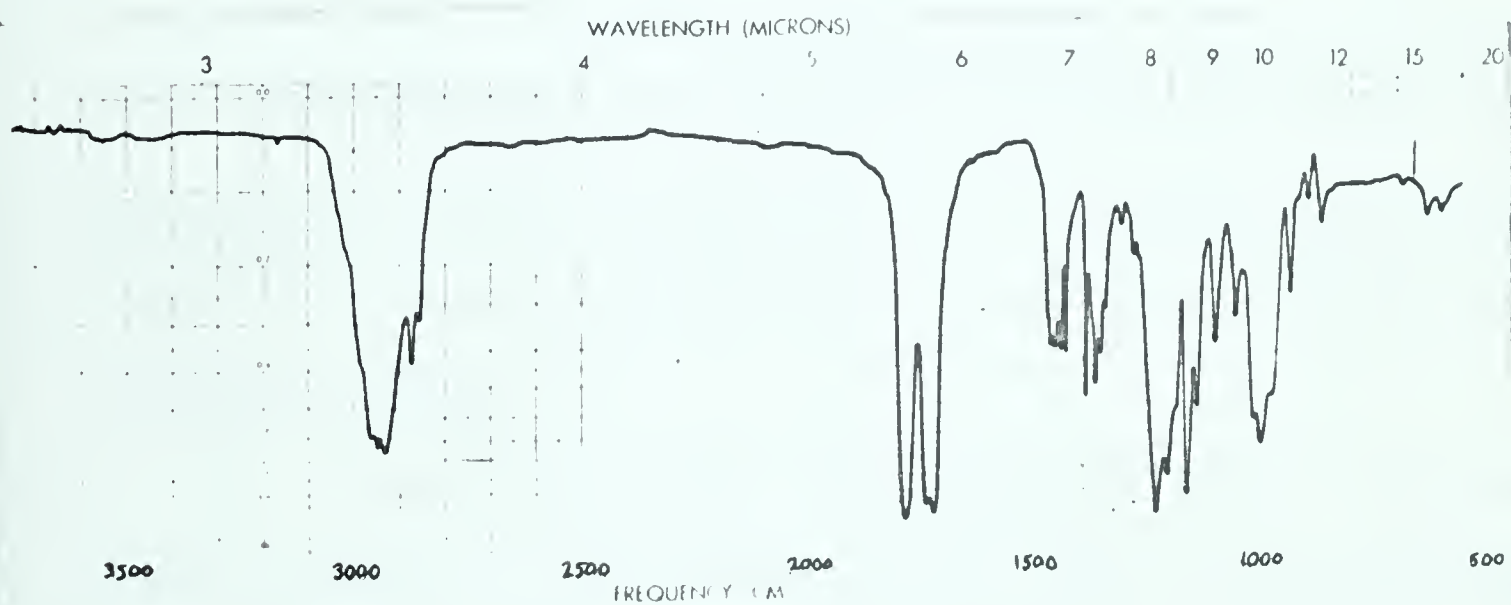
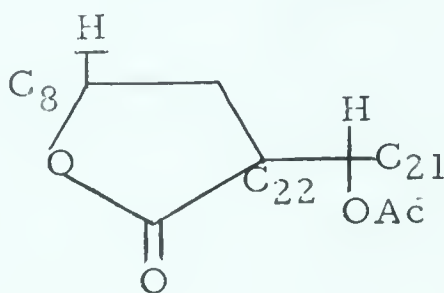


Figure 42. Infrared spectrum of lactone I.

The infrared spectrum of lactone I showed a carbonyl band at 1784 cm^{-1} (CCl_4 solution; 1775 cm^{-1} in CHCl_3) which is attributed to a five membered lactone ring. A sharp one proton signal at 5.19τ in the n.m.r. spectrum is assigned to a proton attached to the same carbon as the lactone ethereal oxygen. This information is best accommodated by postulating a ring closure between the carboxyl on C-22 and C-8 analogous to the lactonization observed in the formation of lactone III.

Spectral evidence for the presence of an acetate group in lactone I is provided by a band at 1740 cm^{-1} in the infrared spectrum and in the n.m.r. spectrum by a three proton signal at 7.90τ . Previous studies on acetate incorporation during lead tetraacetate decarboxylation have shown that, in the absence of rearrangement, the point of attachment is the carbon from which the carboxyl group has been lost^{120,122,126}. Assuming that lactone I does not represent an exception to this generalization and that rearrangement has not occurred the acetoxyl group must be attached to C-21.

The following experimental data confirms the consequences of these assumptions, namely, that lactone I contains a secondary acetate β to the lactone carbonyl (part structure A).



A

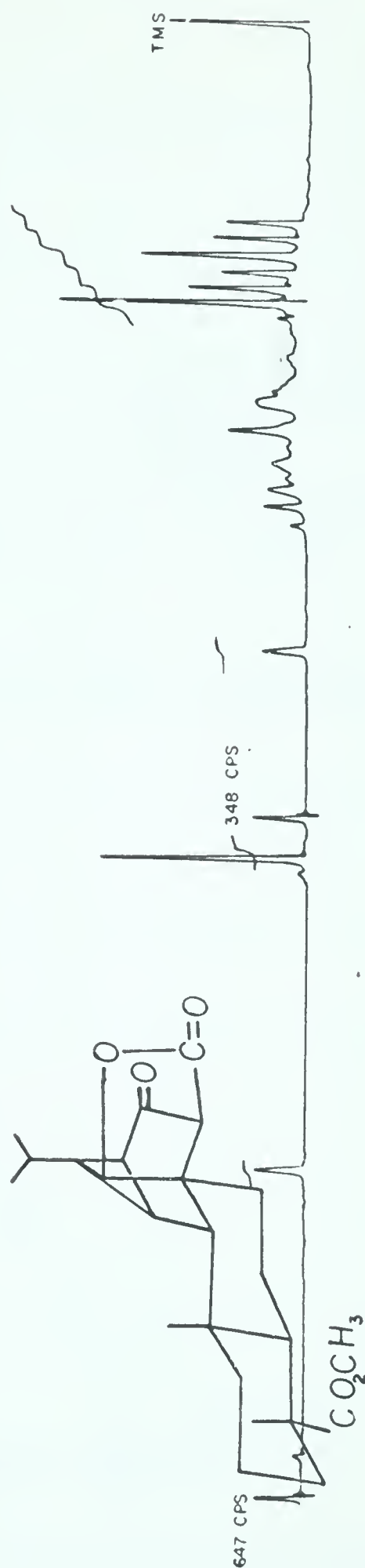


Figure 43. Nuclear magnetic resonance spectrum of the keto lactone 94. at 100 mc.

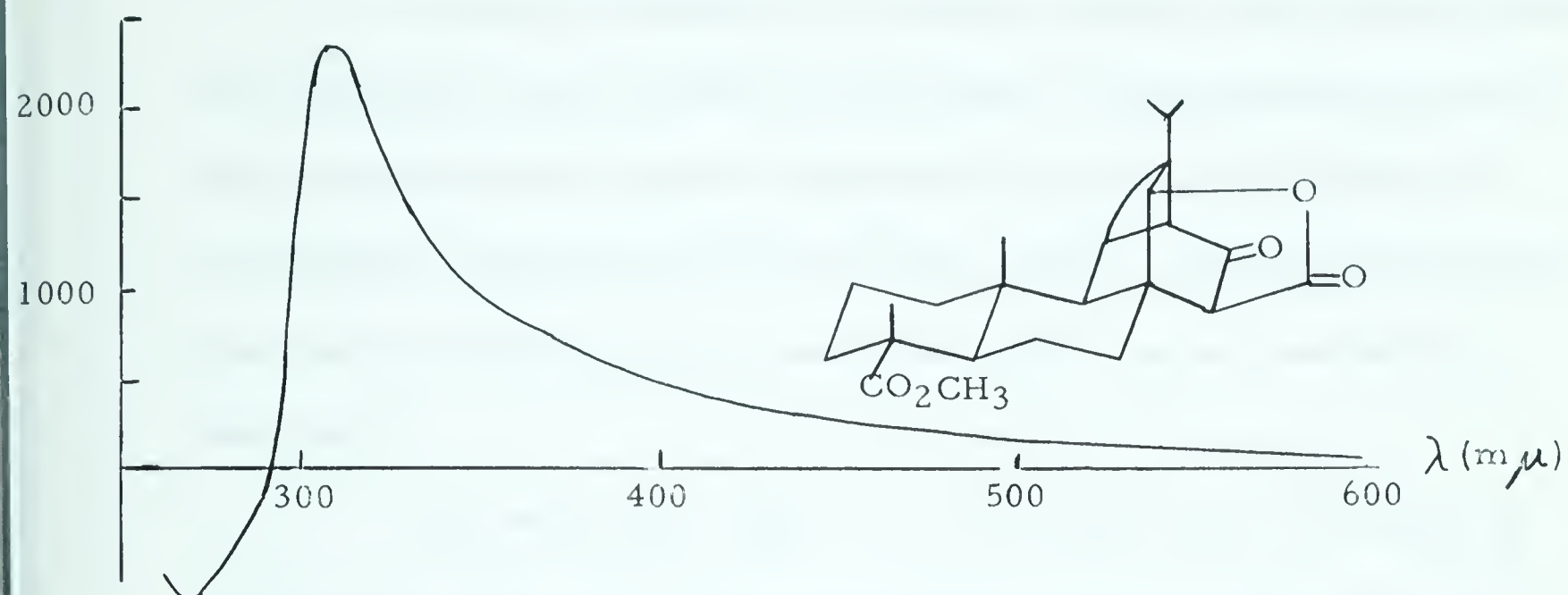


Figure 44. R.D. Curve of the Keto Lactone 94

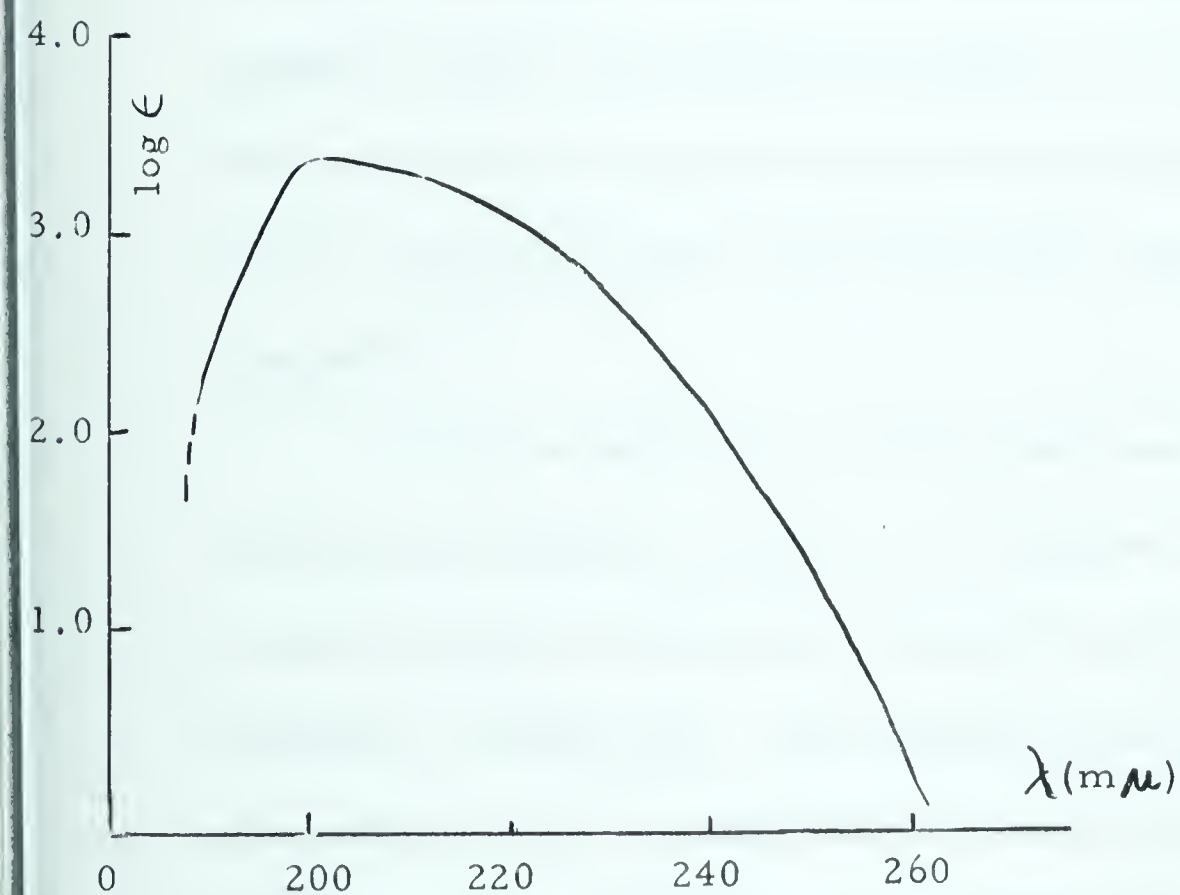


Figure 45. Ultraviolet Spectrum of the Keto Lactone 94

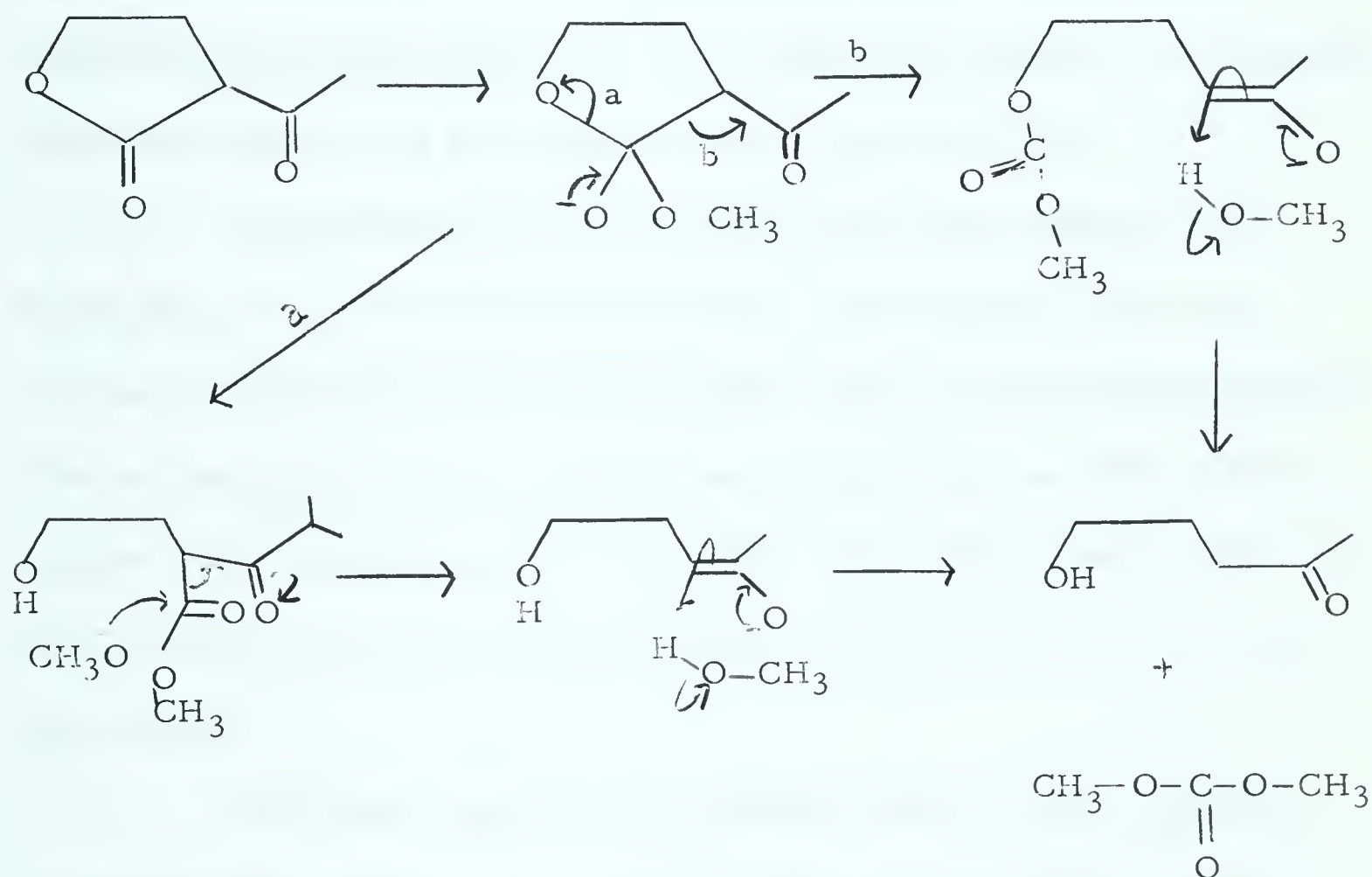
Zemplin methanolysis of lactone I provided the hydroxy lactone 93, $C_{24}H_{34}O_5$, m.p. 189-90°C, in 90% yield. The infrared spectrum (CCl_4) possessed two bands in the carbonyl region, one at 1782 cm^{-1} (γ lactone), the other at 1729 cm^{-1} (C-1 ester). The hydroxyl function was characterized by a sharp peak at 3610 cm^{-1} and a broad band at 3480 cm^{-1} .

The one proton signal at 5.19τ in the n.m.r. spectrum of lactone I was not greatly influenced by this conversion appearing in the hydroxy lactone at 5.24τ . However, a one proton doublet ($J=5\text{ c.p.s.}$) at 4.85τ in lactone I was found to be replaced by a poorly resolved triplet at 5.80τ in the hydroxy lactone 93. This shift upfield establishes the presence of a secondary acetate function since hydroxyl groups are known to deshield protons attached to the same carbon less than do acetoxy groups⁴³.

To establish the relative positions of the acetoxy and lactonic functions the hydroxy lactone 93 was oxidized with potassium dichromate in acetic acid to the dimorphic ketolactone 94, $C_{24}H_{32}O_5$, m.p. 179-80°C; 184-85°C, in 88% yield. The infrared spectrum was free of hydroxyl absorption but now contained three bands in the carbonyl region (1790 (γ lactone), 1725 (C-1 ester) and 1715 cm^{-1} (ketone)). The u.v. spectrum ($\lambda_{\text{max}}\ 286\text{ m}\mu$ ($\epsilon = 82$)) and RD curve (positive Cotton effect $[M]_{303} +10,700^\circ$) provided further evidence for the presence of a ketonic function in the oxidation product.

Assuming that no structural rearrangements have accompanied

the oxidation, it was anticipated that the keto lactone 94 would be sensitive to base. The predicted product was the hydroxy ketone 95 derived either from a combination of lactone ring opening and reverse Claisen condensation (route a) or reverse Claisen followed by Zemplin methanolysis (route b).



In fact it was found that refluxing the ketolactone in 0.6 molar methanolic sodium hydroxide for 18 hours effected a quantitative conversion to a compound $\text{C}_{23}\text{H}_{34}\text{O}_4$, m.p. 228-29°C, possessing spectral properties expected of the hydroxy ketone 95. Thus the infrared spectrum showed hydroxyl absorption at 3610 cm^{-1} (sharp) and 3450 cm^{-1} (broad) and carbonyl absorption at 1727 cm^{-1} (C-1 ester) and 1687 cm^{-1} (ketone). In

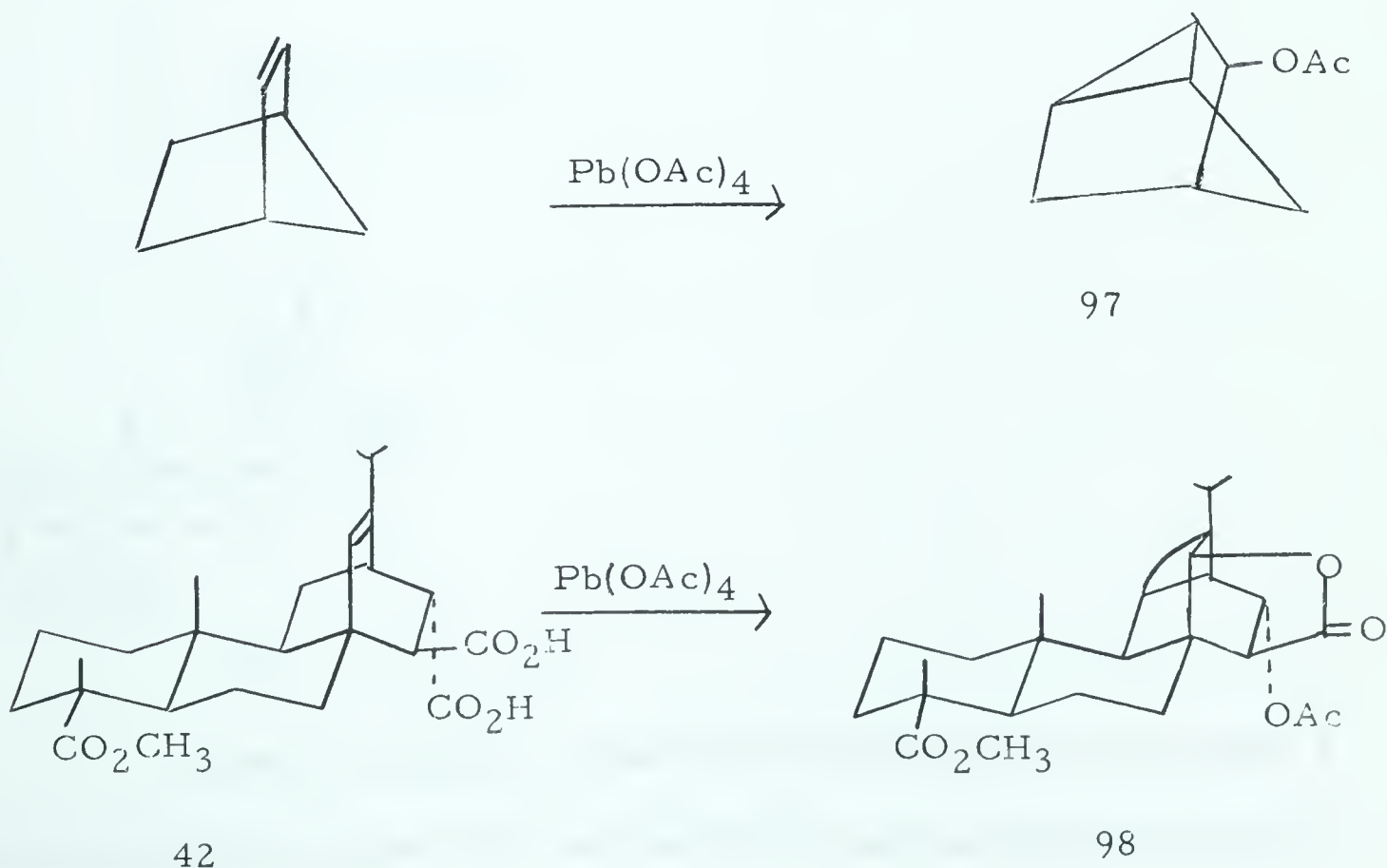
the n.m.r. spectrum the C-8 proton appeared as a singlet at $\tau=5.58$ and the C-1 ester as a three proton signal at 6.32τ . The n.m.r. spectrum showed a 1 proton signal at 7.36τ in 20% CHCl_3 which was found to shift upfield to 7.87τ in 10% solution. The dependence of hydroxyl chemical shift values on concentration is well known¹²⁹, hence this observation provides further confirmation for the presence of a hydroxyl proton in the ketone 95. The ultraviolet spectrum, as expected, exhibited a weak $n \rightarrow \pi^*$ transition at $275 \text{ m}\mu$ ($\epsilon = 50$).

Conversion of the hydroxy ketone 95 to the diketone 96, $\text{C}_{23}\text{H}_{32}\text{O}_4$, m.p. $178-79^\circ\text{C}$ with potassium dichromate in acetic acid provided chemical proof for the secondary nature of the hydroxyl function. The infrared spectrum of 96 showed no absorption above 3000 cm^{-1} but contained two carbonyl bands, one at 1727 cm^{-1} , the second at 1715 cm^{-1} . The ultraviolet spectrum revealed broad $n \rightarrow \pi^*$ absorption at $273-287 \text{ m}\mu$ ($\epsilon = 90$).

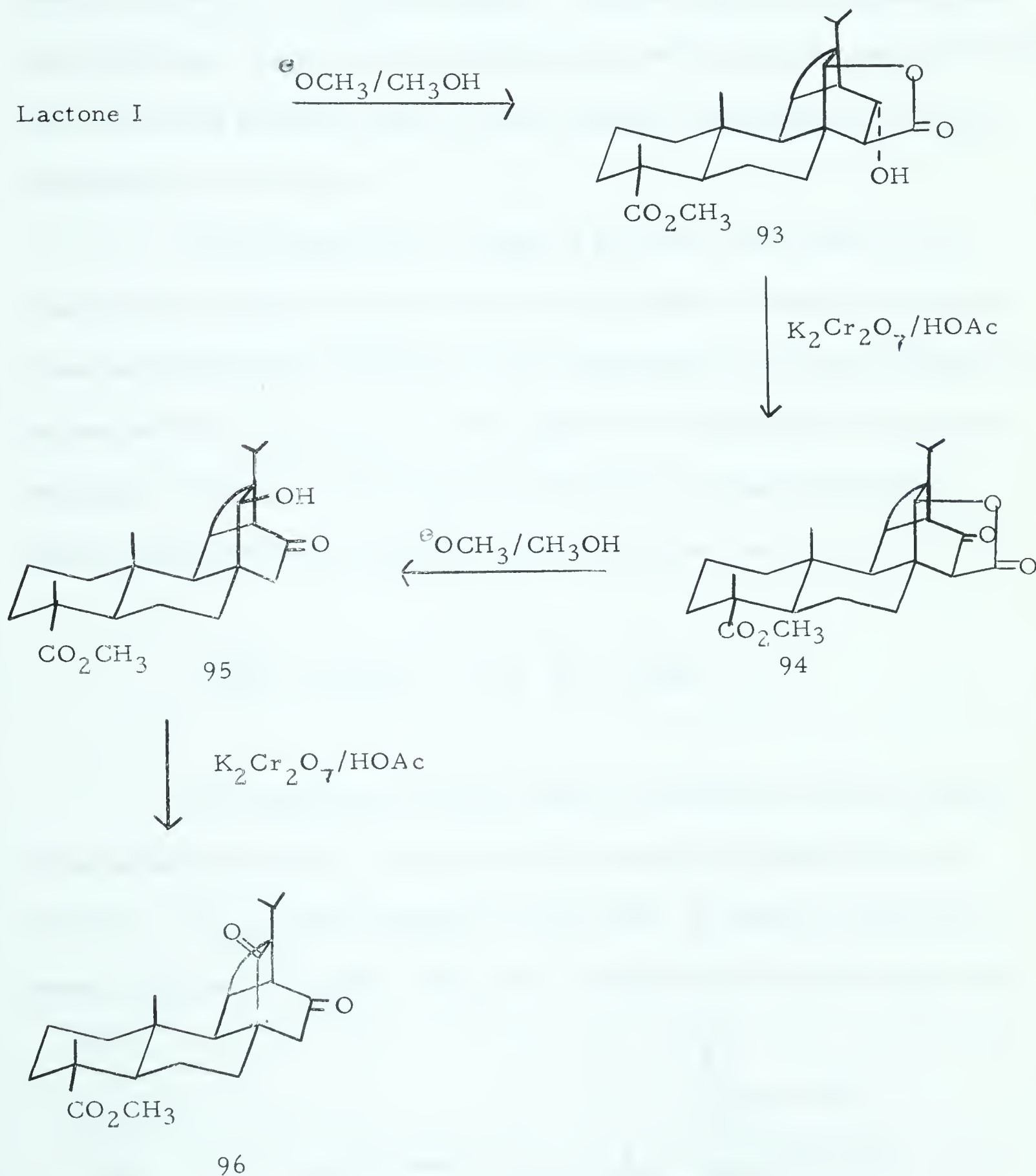
The mass spectrum of the diketone did not show extensive ionization in the high molecular weight region, consequently, an exact molecular weight measurement could not be obtained. However, the range of possible values (370 ± 2) was in harmony with the value of 372 calculated from the elemental analysis. This molecular weight determination receives additional support from the elemental analysis of the preceeding derivatives 93, 94 and 95 and hence confirms the original contention that conversion of the diacid 42 to lactone I is accompanied by the oxidative removal of two hydrogens.

From these initial observations it appeared unlikely that lactone I contained an olefinic bond. Thus the only two signals in the n.m.r. spectrum of lactone I at sufficiently low field to be considered as possibilities for vinyl hydrogens (4.85 and 5.247) have already been adequately accounted for in terms of the part structures $\text{H}-\text{C}^+=\text{OAc}$ and $\text{H}-\text{C}^+=\text{O}-\text{C}(=\text{O})-\text{R}$. The absence of olefinic hydrogens is further supported by the n.m.r. spectra of the derivatives described above. The spectrum of the diketone 96, for example, contained no protons below the three proton C-1 carbomethoxyl peak at 6.367. Lactone I thus appears to contain five carbocyclic rings.

This fact, when considered in the light of the reported conversion of norbornene to 3 acetoxy tricyclene 97 with lead tetraacetate in benzene¹³⁰, suggested structure 98 as a possibility for lactone I.



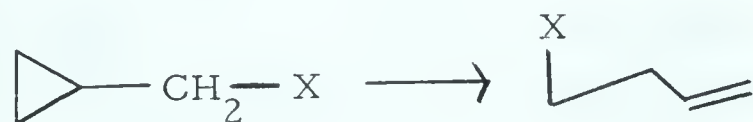
The compounds involved in the transformation sequence just described would then be represented by the following structures:



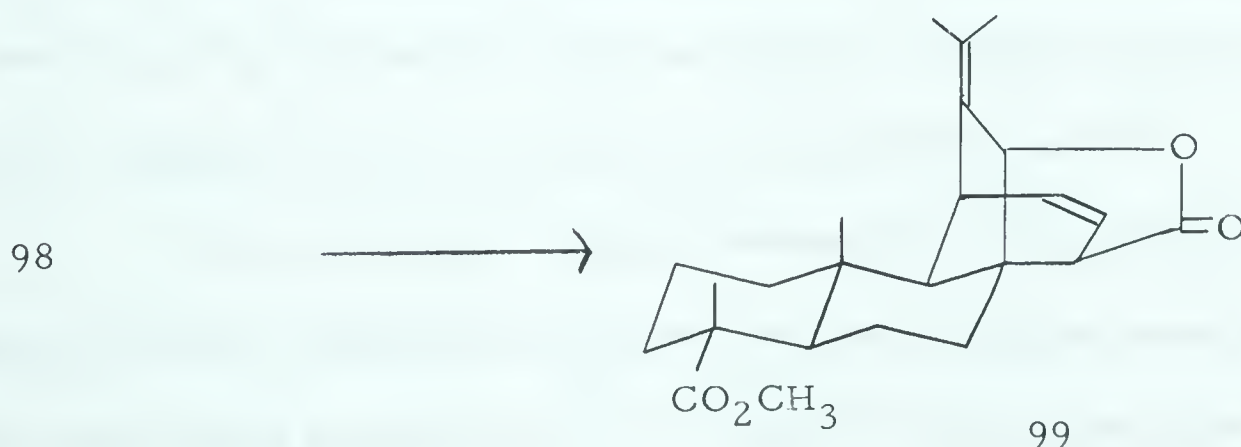
In order to obtain support for this formulation of lactone I the ultraviolet spectrum of the keto ester 94 and the diketone 96 were

examined in the $200\text{ m}\mu$ region. The former exhibited a maximum at $199\text{ m}\mu$; $\epsilon=2400$ (isooc ne) whereas in the diketone 96 the maximum was found at $202\text{ m}\mu$; $\epsilon = 6500$ (CH_3OH). These values are in good agreement with those reported in the literature for $\alpha\beta$ cyclopropyl ketones¹³¹⁻¹³³ and as a result provide support for the presence and location of a cyclopropane ring in lactone I.

In order to test the validity of structure 98, lactone I was reacted with p-toluenesulfonic acid in acetic acid or, better, in benzene. It was anticipated that cleavage of the cyclopropane ring with simultaneous rupture of the C-21 oxygen or C-8 oxygen bond would occur in a manner analogous to that observed for the conversion of cyclopropylcarbinyll benzenesulfonates and chlorides to the allylcarbinyll derivatives^{134,135}.

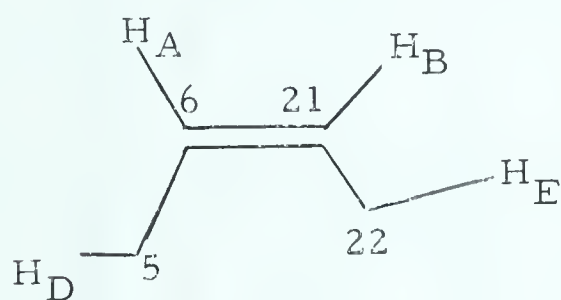


The compound actually isolated (in 90% yield) after 12 hours of refluxing with p-TSA in benzene solution was the diolefin 99, m.p. $171-72\text{ }^\circ\text{C}$; ν_{max} 3042 (olefinic C H), 1765 (γ lactone), 1720 (C-1 ester), 1630 cm^{-1} ($\text{C}=\text{C}$). The n.m.r. spectrum is found on page 222.

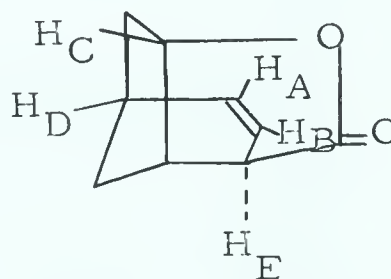


The n.m.r. data, including the results of spin decoupling experiments, are presented in Table VII. The chemical shift values of H_A and H_B together with the fact that they are strongly coupled ($J_{AB} = 8.8$ c.p.s.) indicate the presence of a disubstituted olefin in 99. Since the additional coupling which these protons are involved in is of the order expected for vicinal protons ($J_{AD} = 6.7$; $J_{BE} = 4.8$ c.p.s.) it follows that the diolefin 99 must contain the unit represented by part structure A.

The similarity which J_{AB} and J_{AD} bear to the J_{AX} and J_{AB} couplings of a bicyclooctene system (X = bridgehead methine) is taken as indication for the presence of an identical unit in the diolefin 99 which, in order to meet the requirements of part structure (A) must be the rearranged bicyclo (3.2.1) octene system (B).



A



B

Allylic couplings of the order observed for 99 ($J_{AE} = 1.7$ c.p.s.) are not uncommon. Presumably the normal $\sigma-\pi$ mechanism is involved since H_E approximates the necessary condition that the C-22 H_E bond be coplanar with the π electrons of the double bond^{93b}.

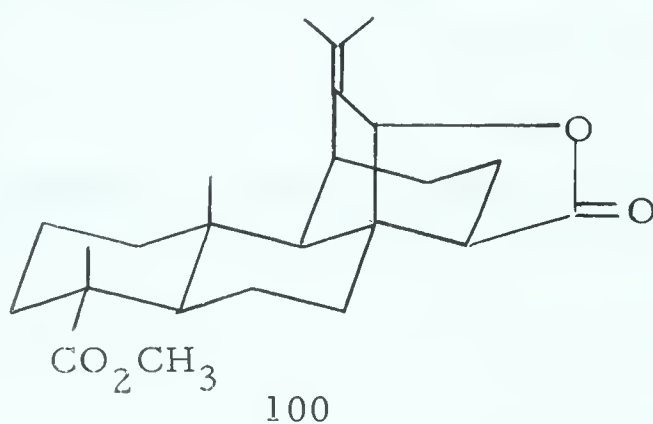
The long range coupling between H_E and H_C ($J_{CE} = 1.7$ c.p.s.) meets the steric requirement that the two interacting protons and the three intervening carbons (C-22, C-14 and C-8) be in the form of a "W",

TABLE VII
CHEMICAL SHIFTS AND COUPLING CONSTANTS ASSOCIATED WITH THE DIOLEFIN 99.

Proton	H _A	H _B	H _C	H _D	H _E	C-19, C-20	C-16	C-17	C-1 CO ₂ CH ₃
Chemical Shift	3.56(1)	4.48(1)	4.93(1)	6.99	7.06	8.23(3) 8.32(3)	8.81(3)	9.25(3)	6.33(3)
Multiplicity	septet	quartet	broad singlet	broad doublet	sextet				
Coupling (c.p.s.)	J _{AE} = 1.7 J _{AB} = 8.8 J _{AD} = 6.7	J _{AB} = 8.8 J _{BE} = 4.8			J _{BE} = 4.8 J _{CE} = 1.7 J _{AE} = 1.7				

an arrangement which appears to be particularly favourable for the transmission of spin information, presumably through the small lobes of the sigma C-H bonds⁷⁶.

The diolefin readily took up one mole of hydrogen to give a quantitative yield of the dihydro derivative 100 ($C_{24}H_{34}O_4$, m.p. 184-185.5°C).



The spectral data clearly indicated that selective hydrogenation of the exposed endocyclic double bond had occurred. Thus the n.m.r. spectrum showed the isopropylidene methyls at 8.26 and 8.32 τ and the shielded angular methyl at 9.29 τ but contained no signal below that of the C-8 proton at 5.00 τ . The olefinic C-H stretching band present at 3042 cm^{-1} in the diolefin 99 was absent in the dihydro derivative 100.

The exo orientation of the C-21 acetoxy group in lactone I is supported by two lines of evidence. First, the concentration dependent nature of the hydroxyl bands at 3610 cm^{-1} and 3480 cm^{-1} suggests intermolecular hydrogen bonding and is therefore more compatible with an exposed exo orientation rather than the alternative configuration where intramolecular hydrogen bonding with the lactonic carbonyl might be

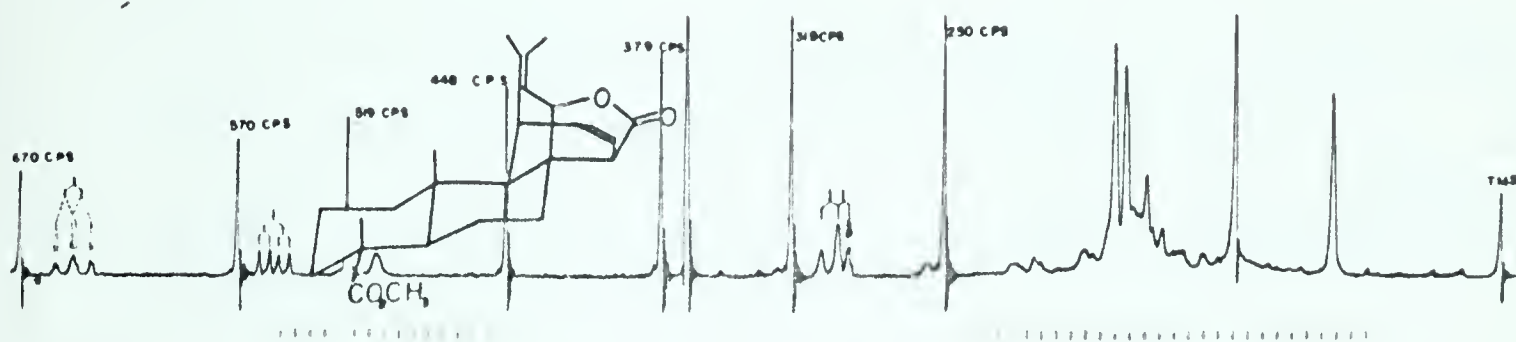


Figure 46. Nuclear magnetic resonance spectrum of the diolefin 99. at 100 mc.

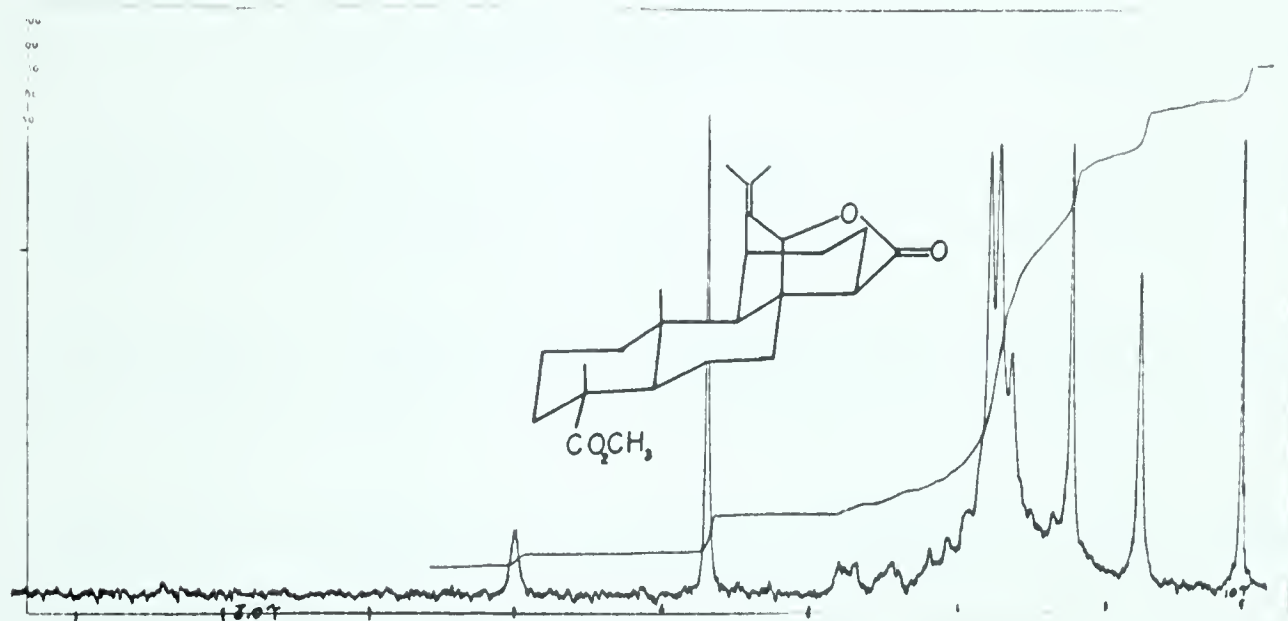


Figure 47. Nuclear magnetic resonance spectrum of the dihydro-diolefin 100.

expected.

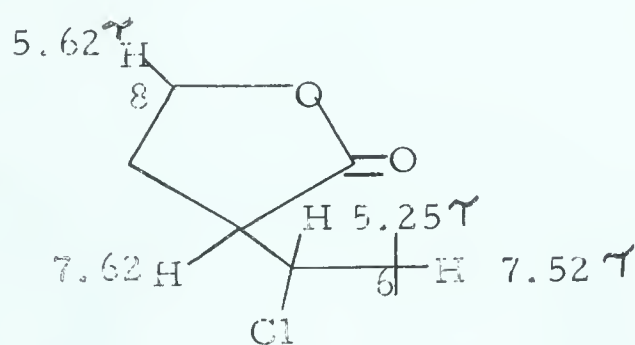
Secondly, from an analysis of the n.m.r. spectra of various bicyclo (2.2.2) octane and octene derivatives it was found that in C-21 endo carbomethoxyl derivatives $J_{H_6H_{21}} = 1-2$ c.p.s. and $J_{H_{21}H_{22}} = 10-12$ c.p.s. while for C-21 exo derivatives $J_{H_6H_{21}}$ and $J_{H_{21}H_{22}}$ both fall in the range of 4-6 c.p.s.¹⁰⁴. In lactone I the C-21 proton was found to be coupled to a proton at 8.24τ ($J = 5$ c.p.s.). Identification of this signal with either the C-6 or C-22 proton is both difficult and unnecessary as the observed coupling whether with the C-22 or C-6 proton is compatible only with an exo orientated acetoxy substituent.

The possibility that the extent of coupling between the bridgehead methine and a C-21 endo proton might be influenced by a distortion of bond angles caused by the introduction of a cyclopropane ring appears unlikely from an inspection of molecular models. Also, the replacement of a C-21 carbomethoxyl by a C-21 acetoxyl group should not invalidate the assignment because the electronegativity change is not expected to decrease the coupling constant by more than 2 c.p.s.
136.

A second example of a decarboxylation which appears to involve the incorporation of a solvent molecule was encountered in the decarboxylation of methyl fumaropimarate with lead tetraacetate in dimethyl sulfoxide. The semi-solid product, which could not be purified by recrystallization, yielded, after chromatography on acid washed

alumina, an as yet unidentified neutral compound, melting point 185-86°C, which analyzed for $C_{24}H_{32}O_4Cl_2$. The infrared spectrum showed a lactone band at 1786 cm^{-1} and the C-15 ester function as a strong band at 1720 cm^{-1} . The n.m.r. spectrum showed a 1 proton signal at 5.25τ , coupled to protons at 7.52 and 7.62τ ($J=4.2$ and 1.4 c.p.s. respectively), which is considered to result from a coupling of the C-21 proton (deshielded by a chloride substituent) with the adjacent hydrogens at C-6 and C-22. The later proton also showed a small coupling with a one proton signal at 5.62τ .

This observation appears to be best explained by assuming a long range coupling between the C-8 and C-22 hydrogen, which, if correct, leads to the following part structure.



Although the mode of chloride incorporation is not established it is suspected that an unstable dimethyl sulfoxide adduct is initially formed (see experimental) and that one chlorine atom is incorporated by a direct displacement of sulfoxide at C-21 by a chloride ion during the chromatography on acid-washed alumina.

Incorporation of the second chlorine atom may involve opening of the cyclopropane ring. Some support for this suggestion is found in the fact that the extent of non-equivalence shown by the isopropyl methyls

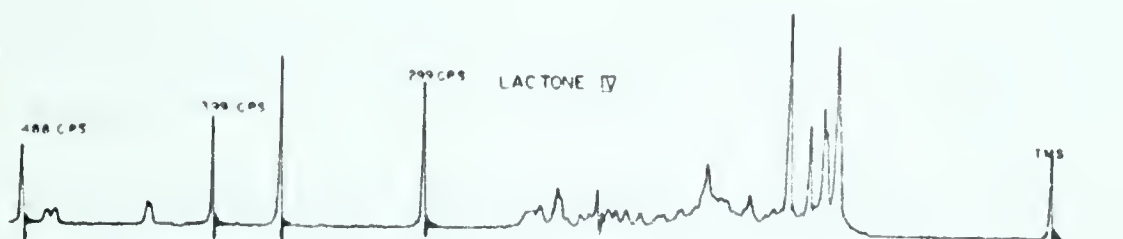


Figure 48. Nuclear magnetic resonance spectrum of lactone IV.
at 100 mc.

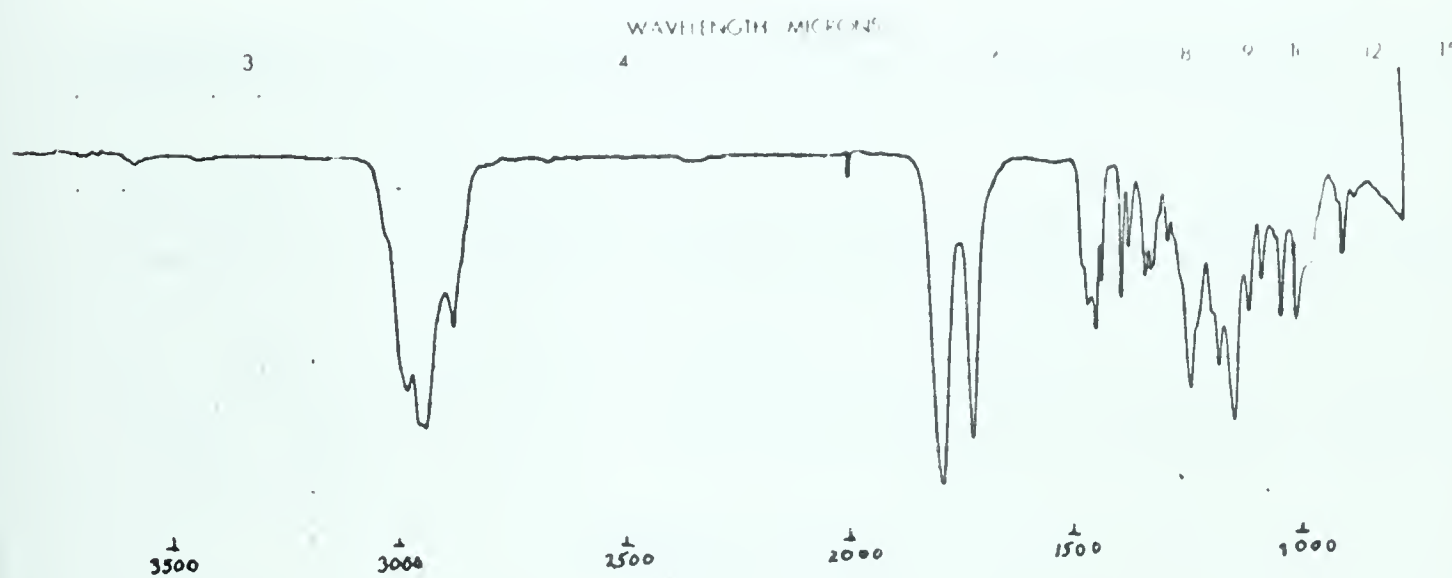
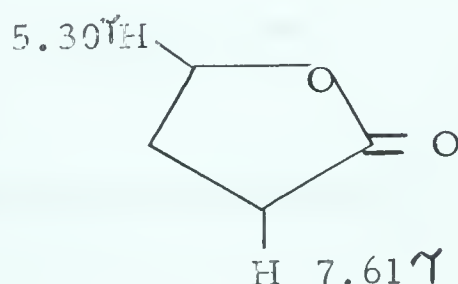


Figure 49. Infrared spectrum of lactone IV.

(0.06 p.p.m.) is closer to that found in the eclipsed C-21 and C-22 carbomethoxyl derivatives 34, 36, 47 and 63 (0.04 p.p.m., see page 83) than in the cyclopropyl compounds described in this section where the chemical shift differences are with two exceptions, the hydroxy ketone 95 (0.14 p.p.m.) and the keto dimethyl ester 105 (0.10 p.p.m., see page 244) in the range 0.2-0.3 p.p.m.. Although the detailed cause of this enhanced nonequivalence in the cyclopropyl compounds (which apparently can be moderated by the presence of a keto group in the molecule) is not understood its absence in lactone IV does suggest that this compound does not contain a cyclopropane ring.

Lactone II - Structure Elucidation

Lactone II, m.p. 176-80°C, analyzed for the molecular formula $C_{24}H_{34}O_4$ and hence is similar to lactone I in that it contains one more unsaturation than the diacid 42. Further parallels can be found in a comparison of the spectral characteristics of lactones I and II. Thus a γ lactone is suggested by a band in the infrared at 1780 cm^{-1} (CCl_4) and in the n.m.r. spectrum by one proton signals at 5.30 and 7.61 τ .



The isopropyl methyls exhibited an even greater degree of non-equivalence than found in lactone I, giving rise to doublets at 8.96 τ

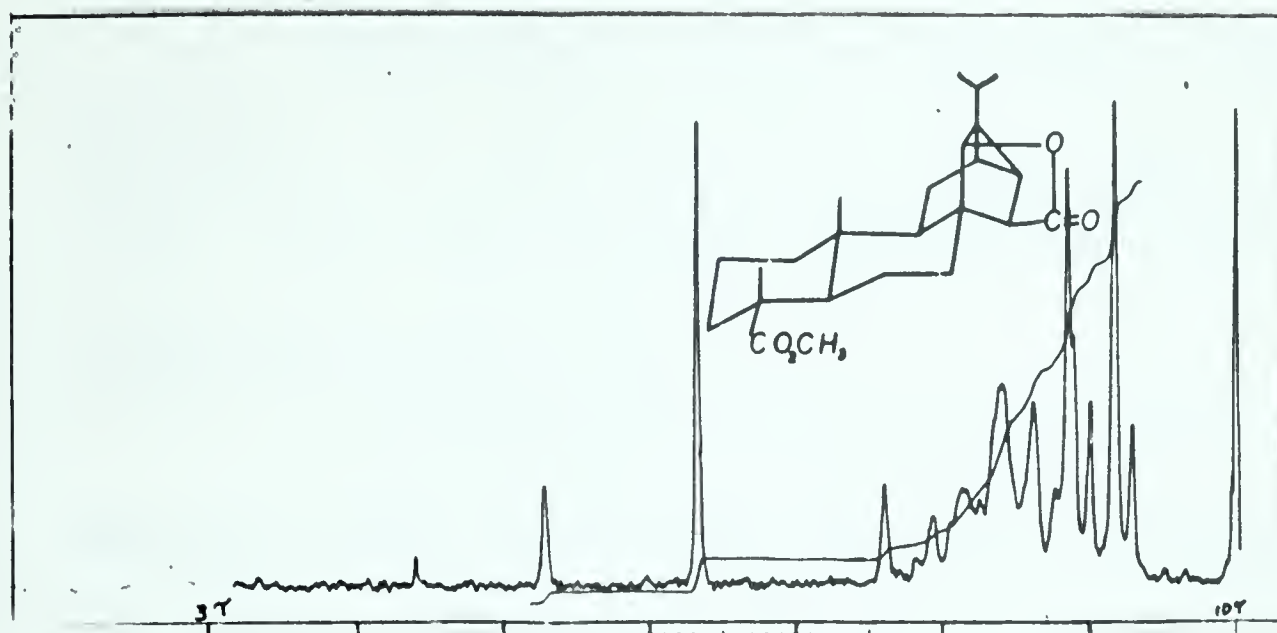


Figure 50. Nuclear magnetic resonance spectrum of lactone II.

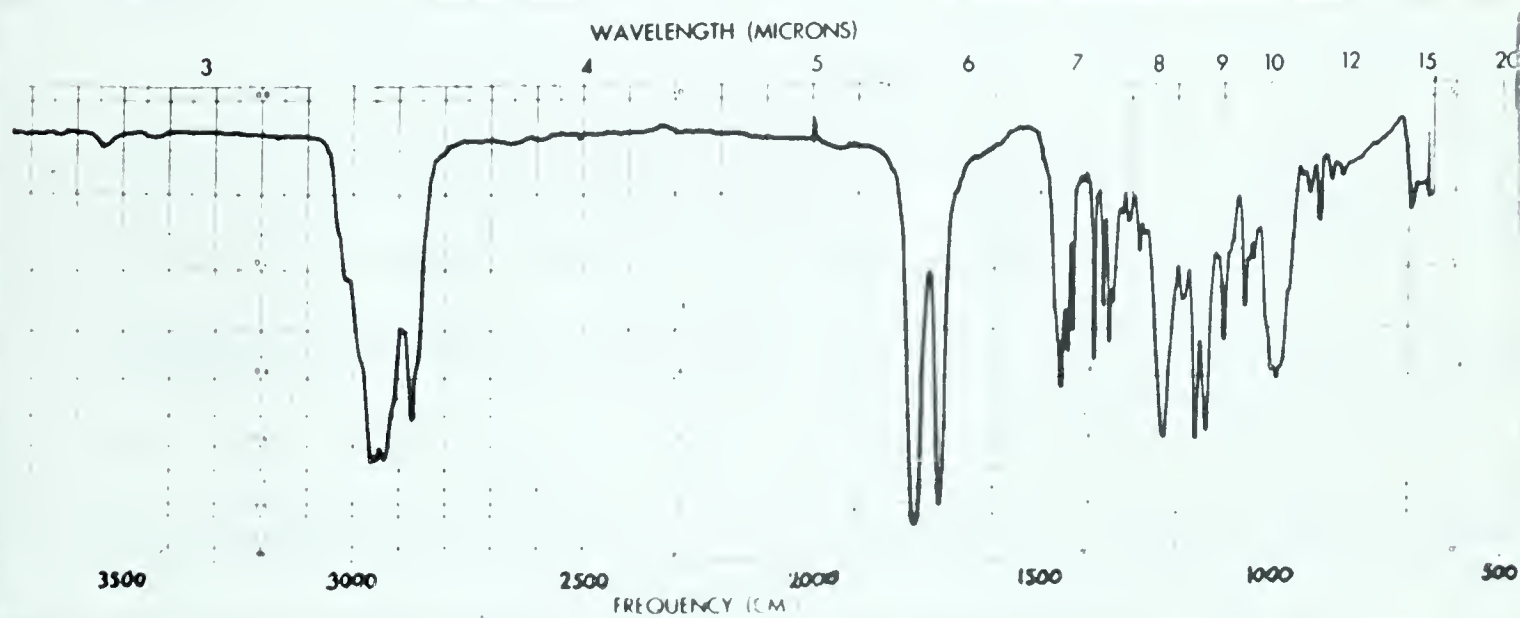


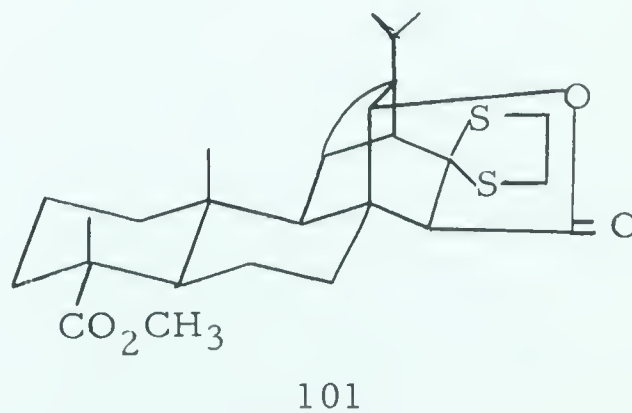
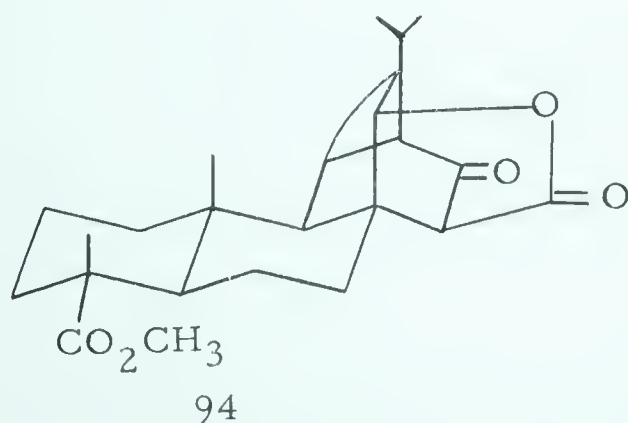
Figure 51. Infrared spectrum of lactone II.

($J=7.5$ c.p.s.) and 9.24τ ($J=7.5$ c.p.s.).

Other points of similarity with lactone I include infrared absorption at 1720 cm^{-1} and a 3 proton n.m.r. signal at 6.33τ assigned to the carbomethoxyl group at C-1 and a C-methyl signal at 9.17τ assigned to the angular methyl at C-12.

Consideration of this information led initially to the speculation that lactones I and II might differ only in the substitution at C-21, loss of the C-21 carboxyl followed by incorporation of an acetoxy group forming lactone I and saturation by hydrogen abstraction leading to lactone II. This simple relationship, however, was disproved by the following two step conversion of the keto lactone 94 to the C-21 methylene derivative 102.

Room temperature reaction of the keto lactone with a ten-fold excess of ethandithiol in boron trifluoride etherate provided a 58% yield of the crystalline thioketal 101, $\text{C}_{26}\text{H}_{36}\text{O}_4\text{S}_2$, m.p. $238-39^\circ\text{C}$. The thioketal function was identified by the presence in the n.m.r. spectrum of a four proton A_2B_2 multiplet centered at 6.6τ . Desulfurization was accomplished by refluxing the 1,3-dithiolane with W-2 Raney nickel in acetone. The deoxy lactone 102, m.p. $135-37^\circ\text{C}$, obtained in 82% yield, clearly differed from lactone II (infrared and n.m.r. spectral comparison).



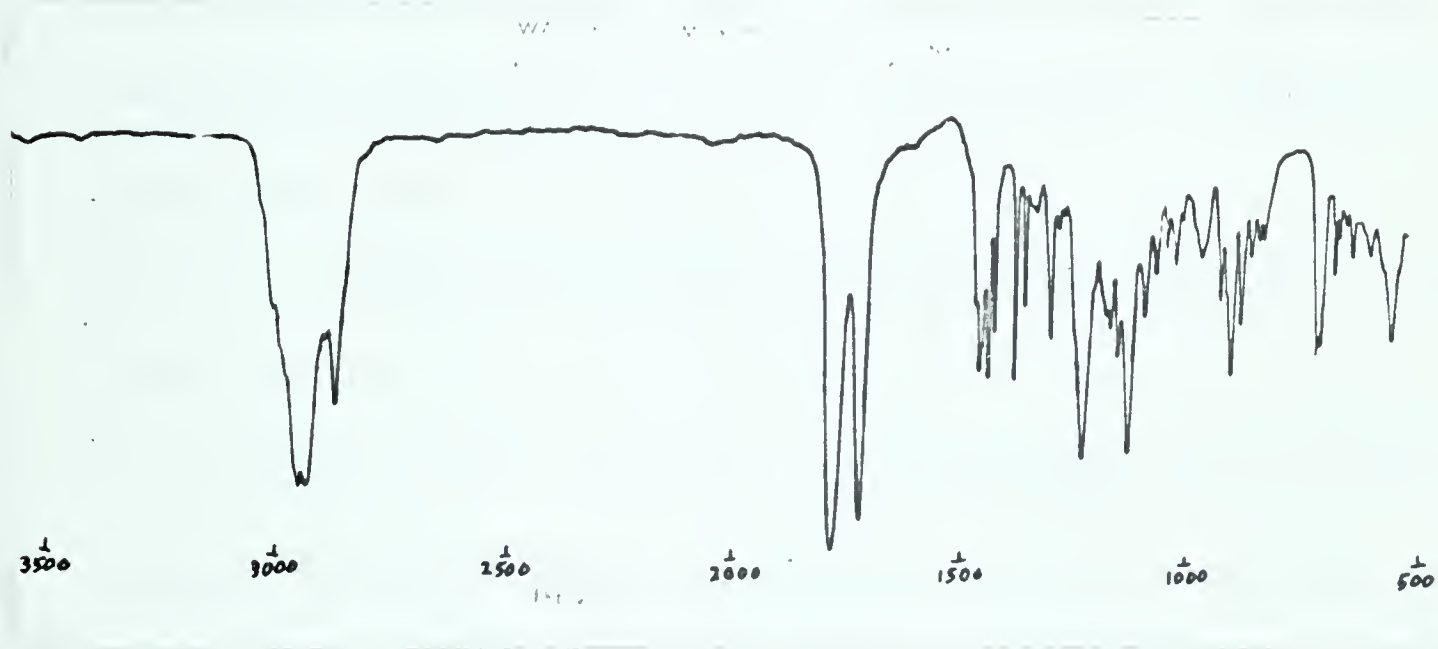
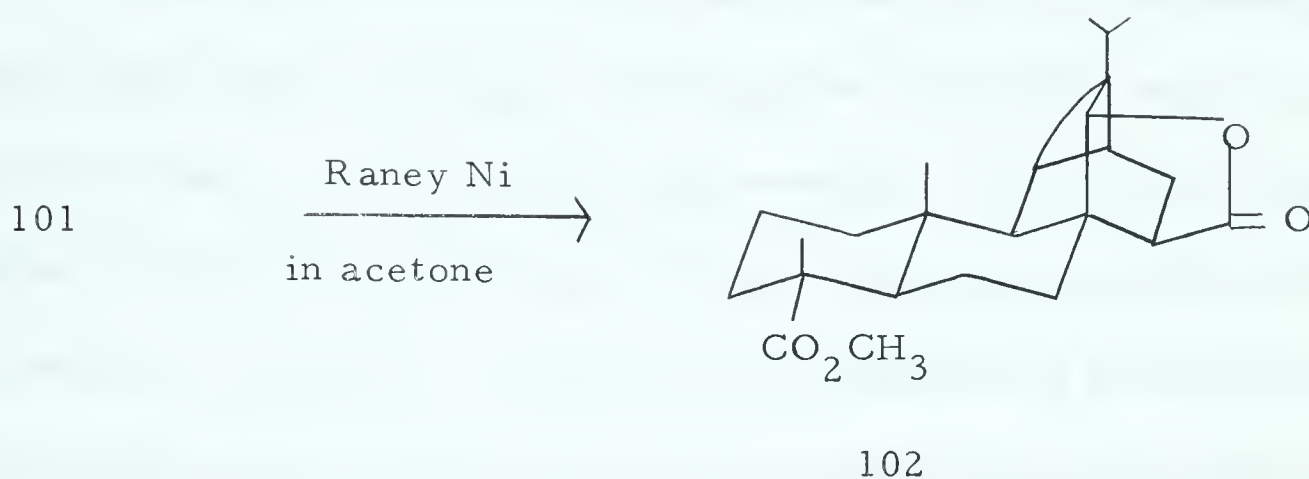
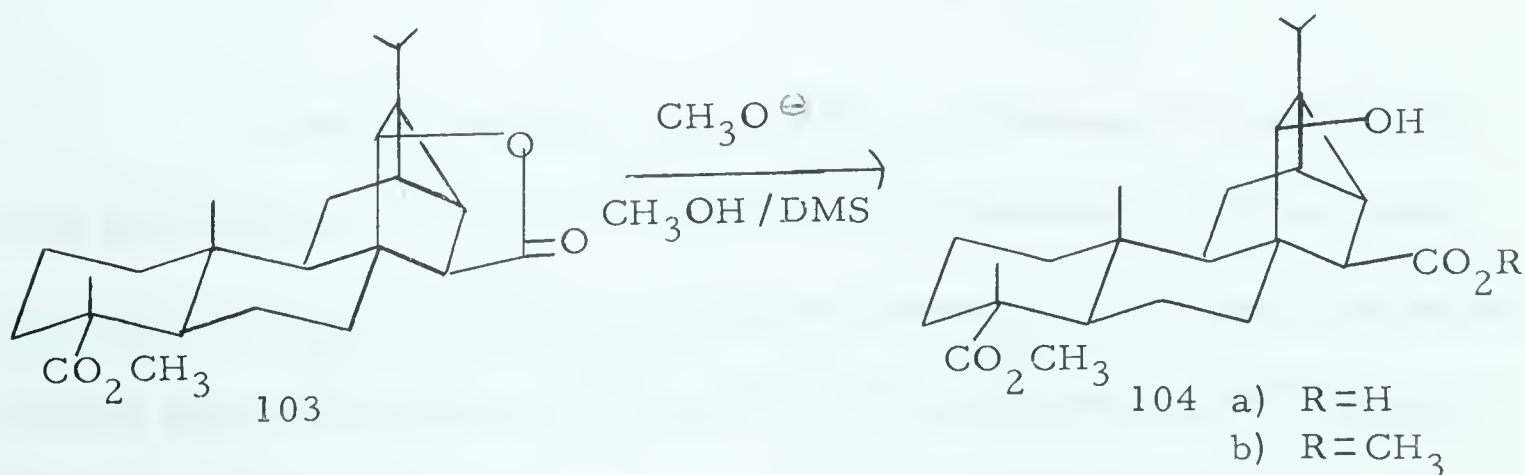


Figure 52. Infrared spectrum of the deoxylactone 102.



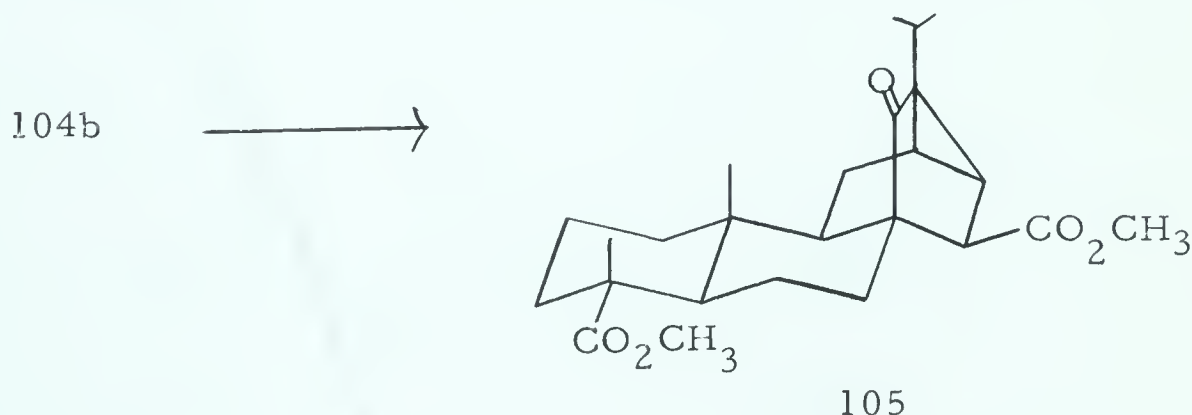
A second possibility involves a lactonization between the carboxyl group at C-22 and C-8 which is accompanied by a cyclopropane ring closure reaction between carbons 6 and 21 (structure 103). In the following paragraphs evidence is presented to support this alternative formulation of lactone II.

A solution of lactone II in dimethyl sulfoxide was converted to the hydroxy acid 104a, melting point 212-15°C, with sodium hydroxide in methanol. That hydrolysis had accompanied opening of the lactone ring was evident from the solubility of the product in aqueous base and by the presence of broad absorption in the $3300\text{-}2400\text{ cm}^{-1}$ region of the infrared spectrum. The secondary hydroxyl group was identified by a sharp one proton signal at 5.72τ in the n.m.r. spectrum and by broad infrared absorption between 3300 and 2400 cm^{-1} .



Conversion of the hydroxy acid 104a to the corresponding dimethyl ester 104b, $C_{25}H_{38}O_5$, melting point, $140-41^{\circ}C$, was accomplished by treatment with ethereal diazomethane. The n.m.r. spectrum revealed a strong coupling between the hydroxyl protons (6.49τ) and the proton on C-8 (6.0τ ; $J = 12$ c.p.s.) confirmed by a deuterium exchange experiment which reduced the AX quartet to a one proton singlet at 6.0τ . An explanation for this phenomenon can be found in the fact that the hydroxyl group is completely intramolecularly hydrogen bonded ($\nu_{\max} 3400\text{ cm}^{-1}$) because it is known that hydrogen bonding can reduce the rate of proton exchange to the point where a vicinal coupling of the hydroxyl proton can be detected¹³⁷. The carbomethoxyl groups of the hydroxy dimethyl 104b were identified by signals at 6.35τ (3H) and 6.41τ (3H).

Conversion of 104b to the keto dimethyl ester 105 was effected by room temperature oxidation with potassium dichromate in acetic acid.



Spectral evidence supporting the presence of a keto group was provided by the infrared spectrum which showed a carbonyl band at 1729 cm^{-1} not present in the hydroxy dimethyl ester 104b in addition to strong ester absorption at 1718 cm^{-1} . The keto diester 105 absorbed

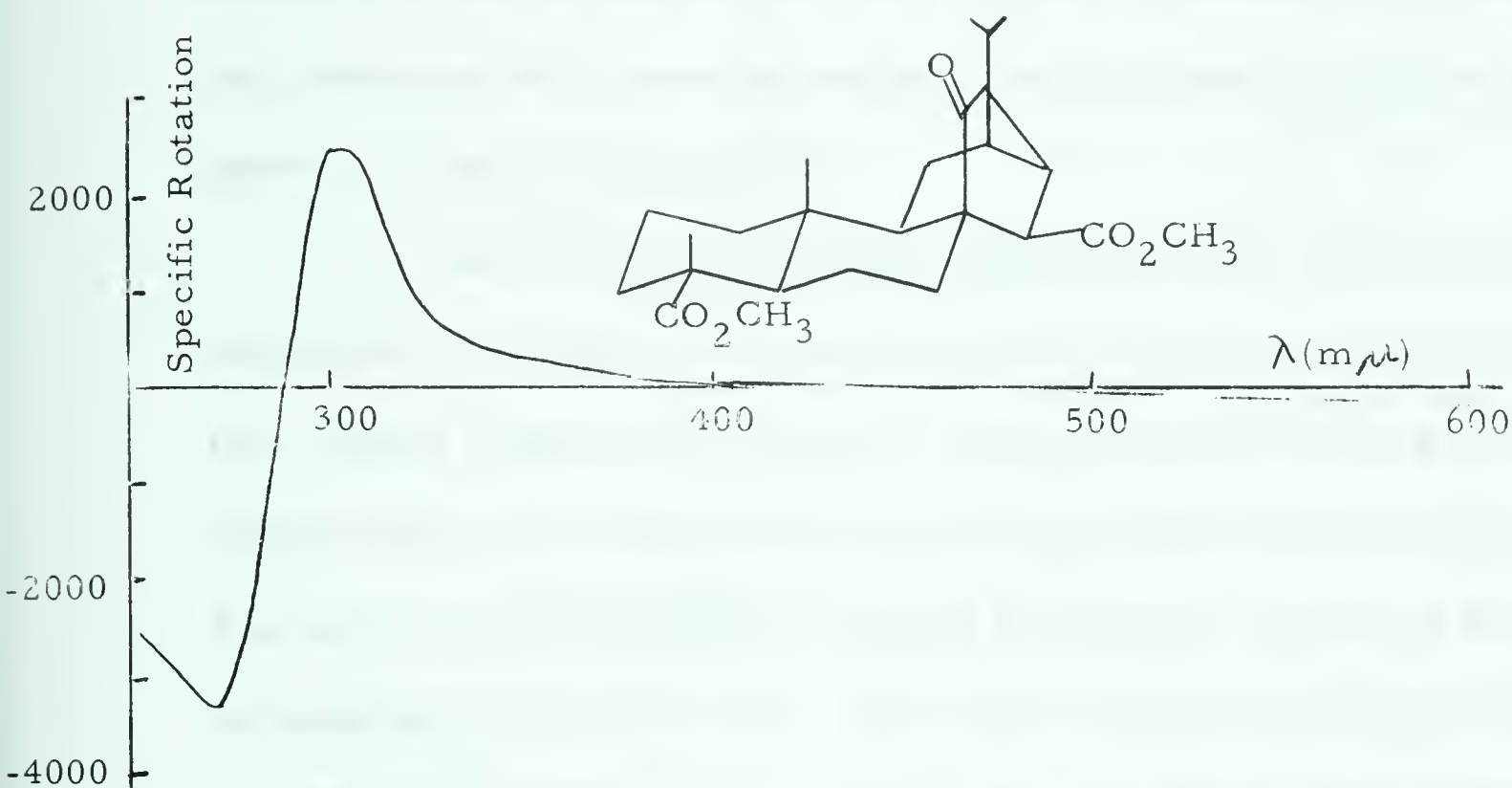


Figure 53. R.D. Curve of the Keto Dimethyl Ester 105

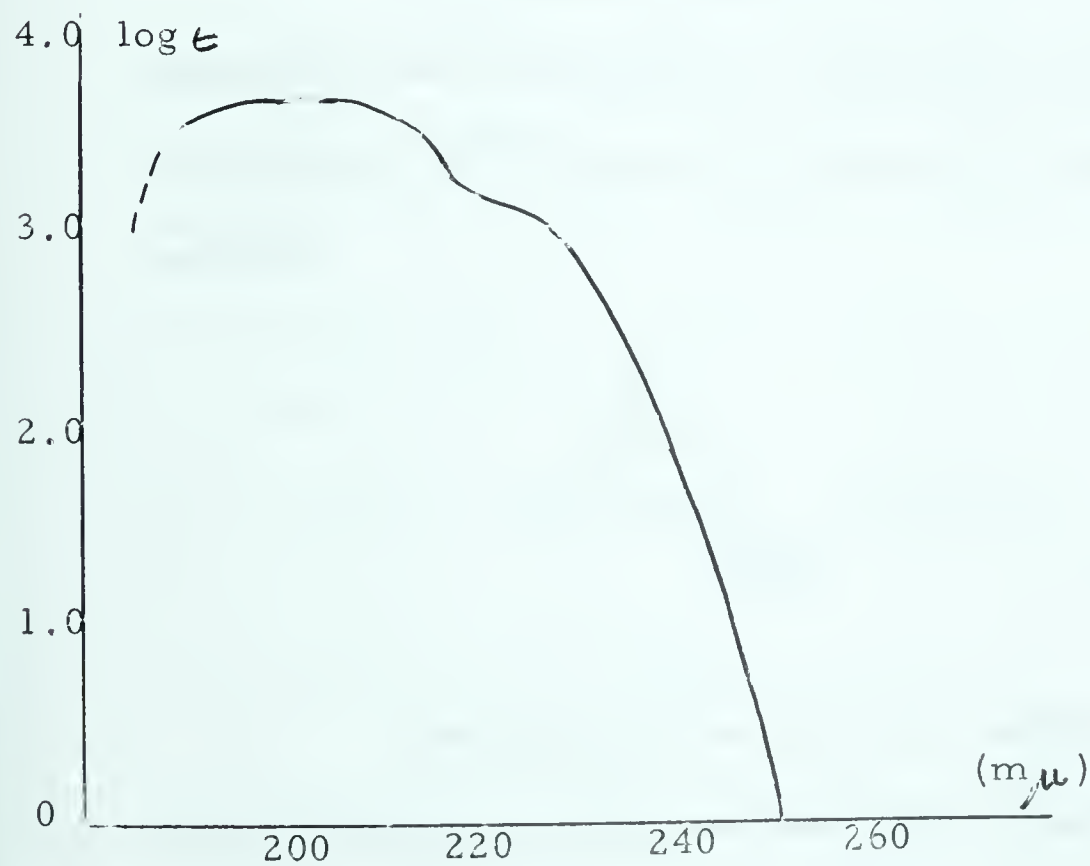
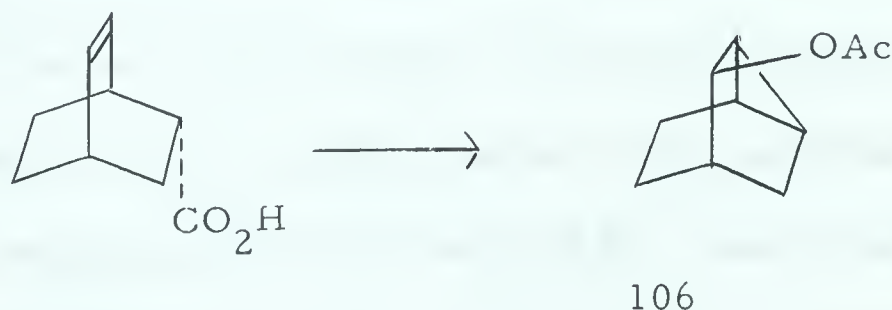


Figure 54. Ultraviolet Spectrum of the Keton Dimethyl Ester 105

in the ultraviolet at $288\text{ m}\mu$ ($\epsilon=70$) and $202\text{ m}\mu$ ($\epsilon = 4000$) thereby establishing the presence of an $\alpha\beta$ cyclopropyl ketone in 105 and, provided the carbon skeleton is unreacted, a cyclopropane ring involving carbon atoms 6, 7 and 21 in lactone II.

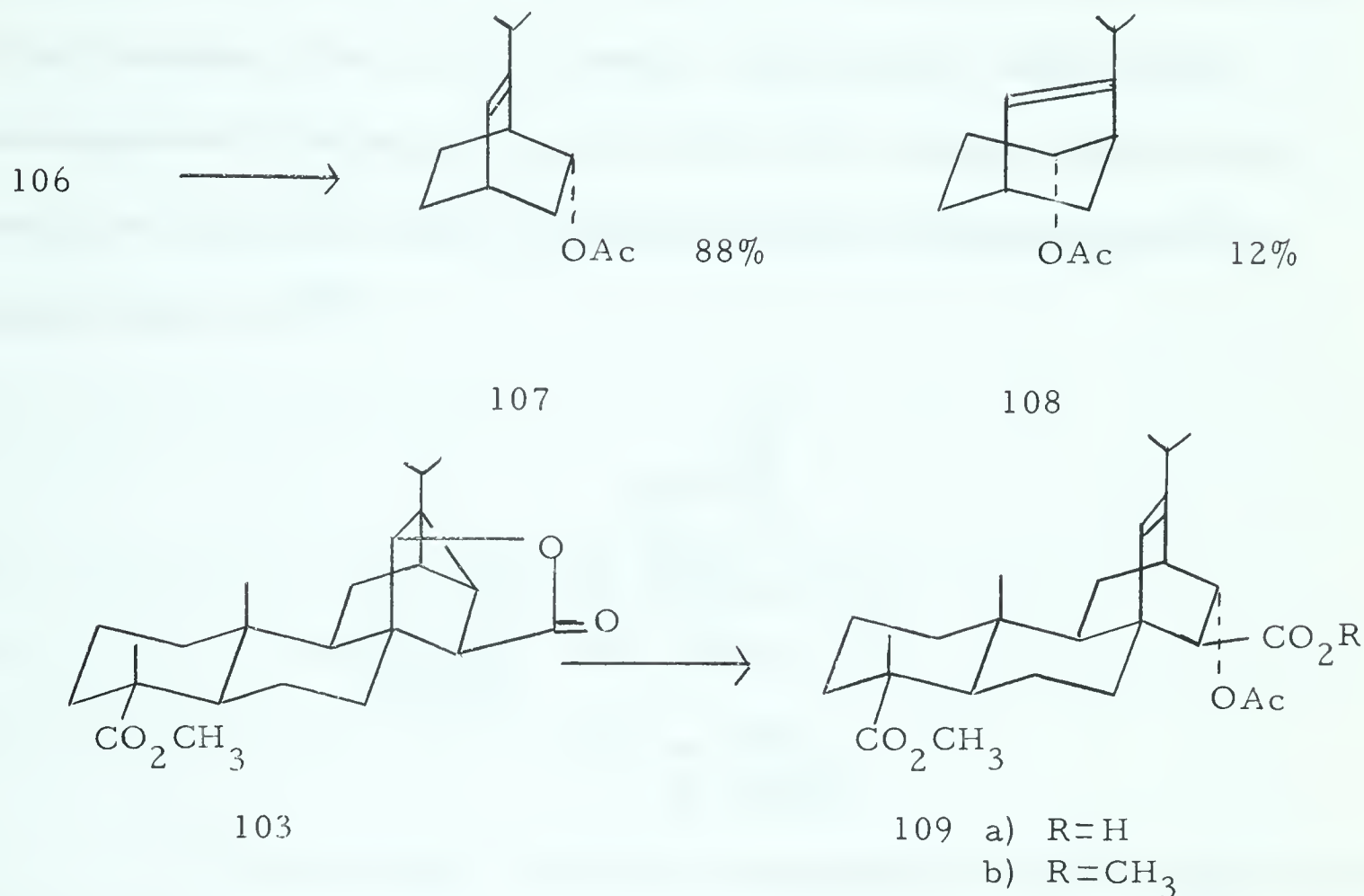
Intrinsically interesting, although of little value in the present structural investigation because of the lack of reference compounds, is the rotatory dispersion curve of 105 which exhibited a strong positive Cotton effect curve with extrema at $303\text{ m}\mu$ ($+10,700$) and $268\text{ m}\mu$ ($-13,800$). The keto lactone 94 (lactone I series) was found to possess a similar strongly positive Cotton effect curve with extrema at $308\text{ m}\mu$ ($+9,500$) and $270\text{ m}\mu$ (-3000) and it is tentatively concluded that this enhanced rotation is due to the cyclopropyl ketone moiety present in both compounds.

The transformation of diacid 42 to lactone II 103 finds a close parallel in the conversion of 5-carboxybicyclo(2.2.2) oct-2-ene to tricyclo(2.2.2.0^{2,6}) octan-3-yl acetate 106 with lead tetraacetate in acetic acid¹³⁸.



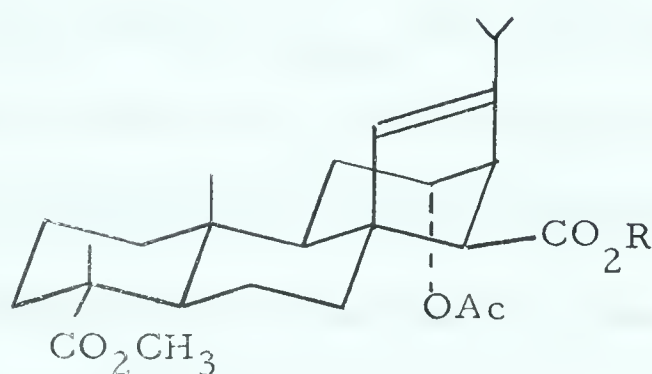
The fact that the tricyclic compound 106 had been transformed by the action of p-toluenesulfonic acid in acetic acid-acetic anhydride, into exo-bicyclo(2.2.2) oct-5-en-2-yl acetate 107 in 88% yield led us to attempt a similar reaction on lactone II in the hope of isolating the acetoxy

acid 109a. A minor product in the above mentioned reaction was the rearranged acetate 108.



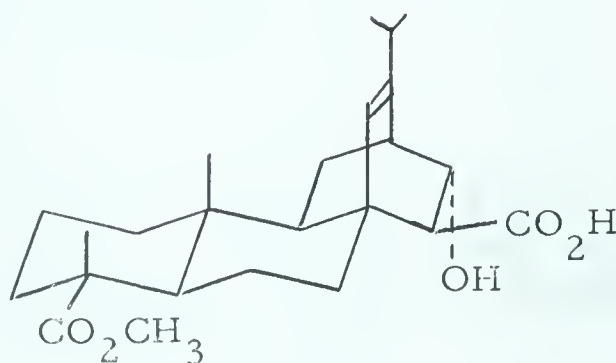
Experimentally it was found that lactone II was extremely sensitive to hot acetic acid being completely converted in less than fifteen minutes to an oily three component mixture (t.l.c. analysis) which from n.m.r. analysis was judged to contain 80% of the acetoxo acid 109a. Thus, predominant restoration of the bicyclo(2.2.2) octene system was indicated by an olefinic peak at 4.63τ (0.84H relative to the carbomethoxyl signal) and a shielded C-methyl group (2.4H) at 9.38τ . Incorporation of a secondary acetoxo function is indicated by a singlet at 8.00τ (3H) and a broad signal (0.8H) at ca. 5.50τ . Infrared absorption between 3300 cm^{-1} and 2500 cm^{-1} and a carboxyl band at 1700 cm^{-1} provide evidence for the presence of a C-22 carboxyl group.

A weak signal in the n.m.r. at 9.23τ (ca. 0.2H) can be attributed to the formation of a bicyclo (3.2.1) octene system resulting from cleavage of the C-6, C-7 bond. This product, 110a, which corresponds to the minor component 108 in the tricyclo octane series, would be expected to shield the angular methyl to approximately the extent observed¹³⁹.



110 a) $R=H$
b) $R=CH_3$

The structure of 109a was established by the following chemical transformation. Treatment of the crude solvolysis product with sodium methoxide in methanol enabled isolation of the major component in the form of the corresponding hydroxy acid 111, m.p. $161-62^\circ C$, in an overall yield of 42%.

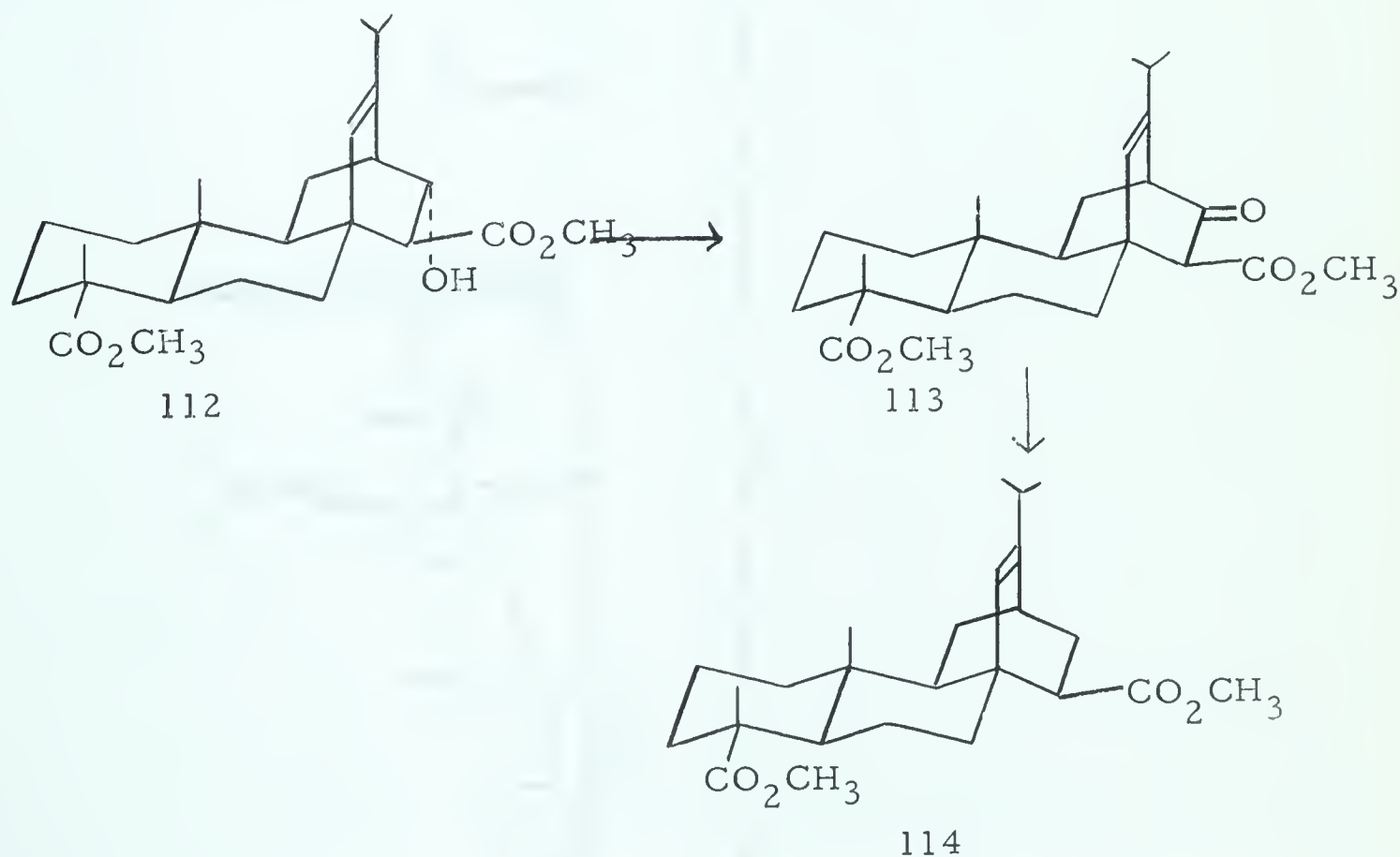


111

The presence of a secondary hydroxyl group was established by absorption in the infrared at 3610 and 3510 cm^{-1} and in the n.m.r.

by a signal at 6.23τ ($H+OH$) replacing that at 5.50τ in the acetylated precursor.

Esterification of 111 with diazomethane provided the hydroxy dimethyl ester 112, $C_{25}H_{38}O_5$, m.p. $135-36^\circ C$; ν_{max} 1715 (s); n.m.r. signals at 6.31τ (3H), 6.40τ (3H), which was easily oxidized with potassium dichromate in acetic acid to the keto diester 113, $C_{25}H_{36}O_5$; m.p. $160.5-161.5^\circ C$; infrared ν_{max} $1722, 1705\text{ cm}^{-1}$; u.v. λ_{max} $296\text{ m}\mu$ ($\epsilon = 139$). Finally, conversion of the keto group to the thioketal derivative with ethanedithiol in $CHCl_3/HCl$, followed by desulfurization with W-2 Raney nickel in 95% ethanol gave the dimethyl ester 114, $C_{25}H_{38}O_4$, m.p. $69-69.5^\circ C$ in an overall 28% yield.



The dimethyl ester was identical by melting point, mixture melting point, n.m.r. and infrared spectral comparison, with an authentic sample of 114 obtained by esterifying the Diels-Alder adduct of levopimaric

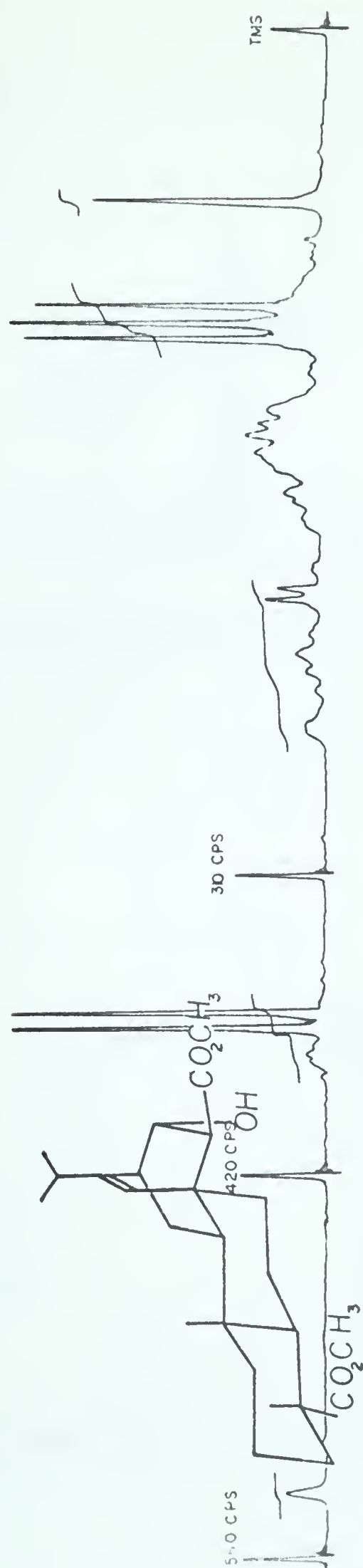


Figure 55. Nuclear magnetic resonance spectrum of the hydroxy dimethyl ester 112. at 100 mc.

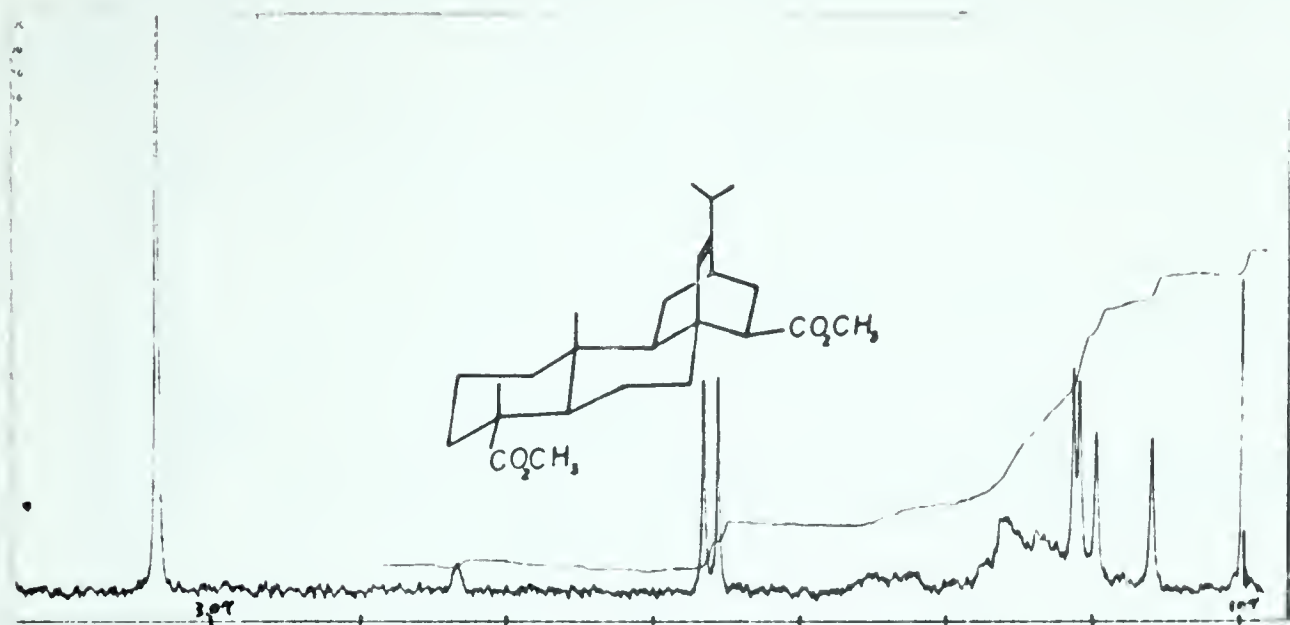


Figure 56. Nuclear magnetic resonance spectrum of the deoxy dimethyl ester 114.



Figure 57. Infrared spectra of the deoxy dimethyl ester 114.

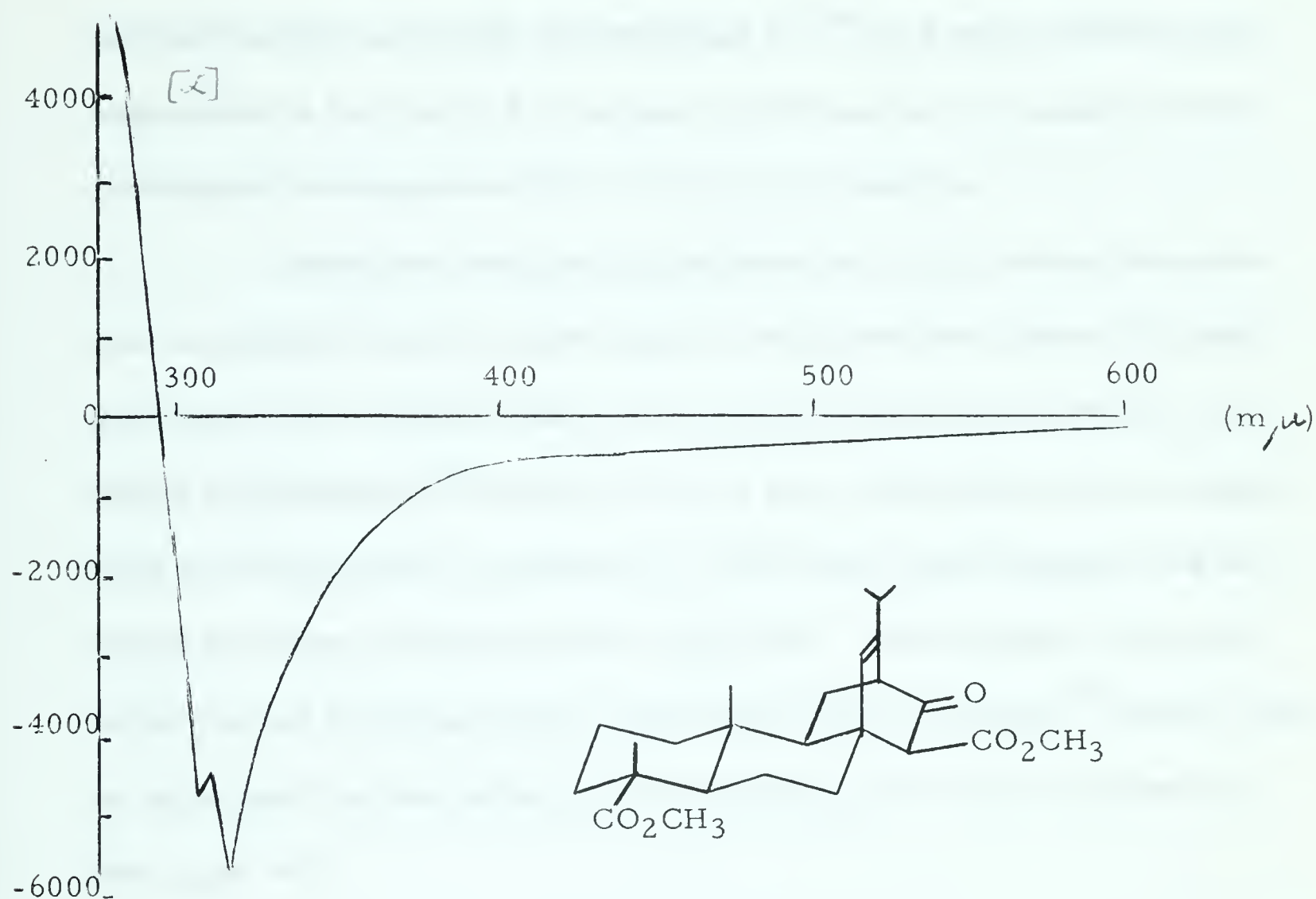


Figure 58. R.D. Curve of the $\beta\gamma$ Unsaturated Ketone 113

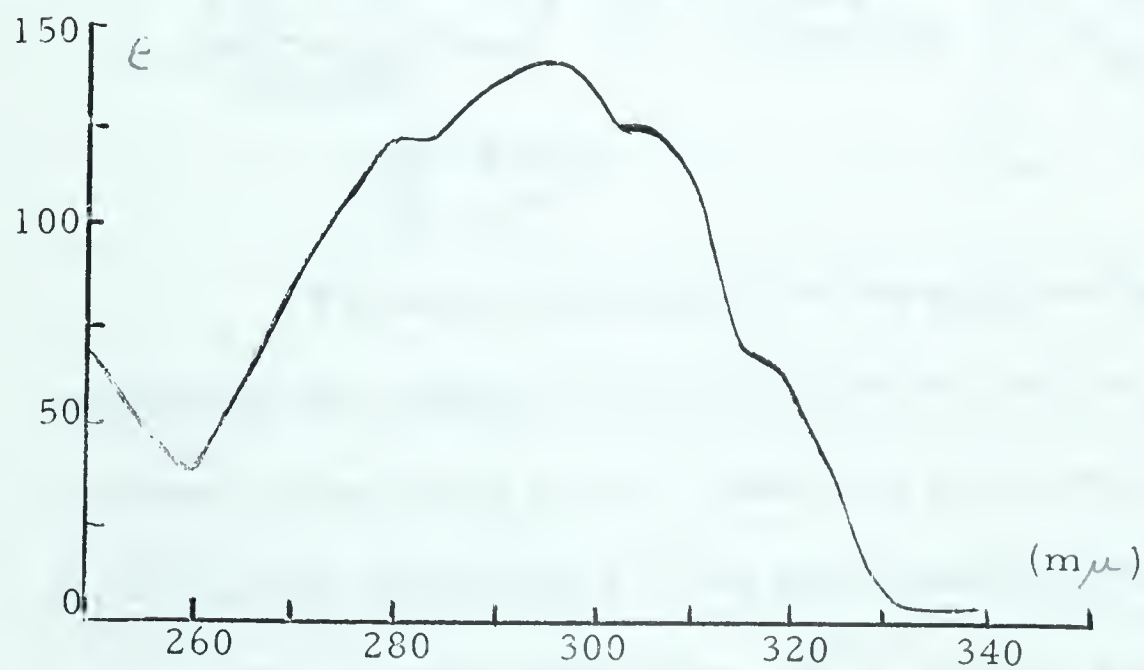
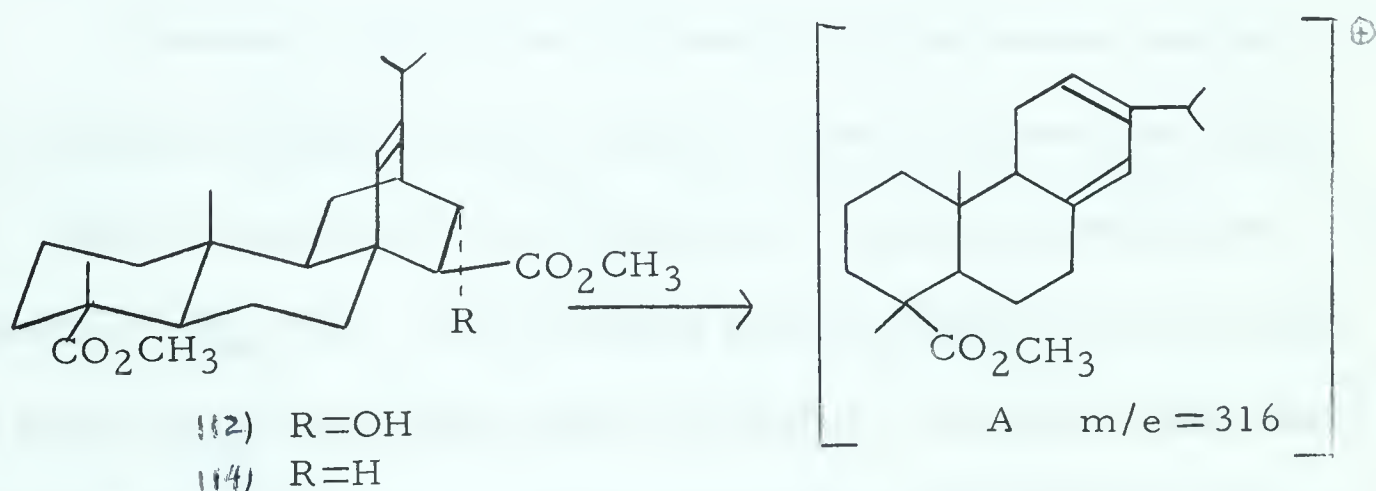


Figure 59. Ultraviolet Spectrum of the $\beta\gamma$ Unsaturated Ketone 113

acid and acrylic acid with diazomethane [†],¹⁴⁰ and hence confirms the presence of a bicyclo (2.2.2) octene system and a C-22 endo carboxyl substituent in compounds 109, 111, 112, 113 and 114.

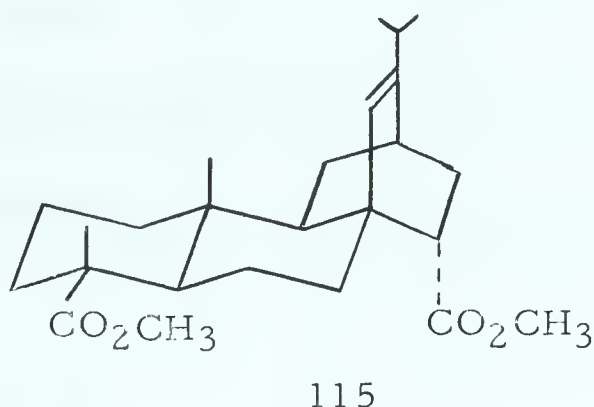
Additional support for the bicyclo (2.2.2) octene structure may be derived from the mass spectra of the hydroxy diester 112 and the diester 114. In the former, the base peak appeared at $m/e = 316$ (6% of total ionization) while in 114 this peak, although not the strongest peak in the spectrum accounted for 3.5% of the total ionization and was by far the most prominent above $m/e = 150$. These peaks correspond to the ion (A) resulting from a retro Diels-Alder reaction¹⁰⁰ known to be an important fragmentation path in bicyclo (2.2.2) octene derivatives. (See page 97).



Further confirmation for the endo configuration of the C-22 substituent was obtained from the chemical shift values of the C-22 carbomethoxyl group in the n.m.r. spectra of compounds 112, 113 and 114. From earlier observations it had been concluded that a C-21 or C-22 carbomethoxyl group endo to the $\Delta^{7,8}$ olefinic bond is shifted upfield by ca. 0.05 τ units from its normal value of 6.35 τ whereas in the exo

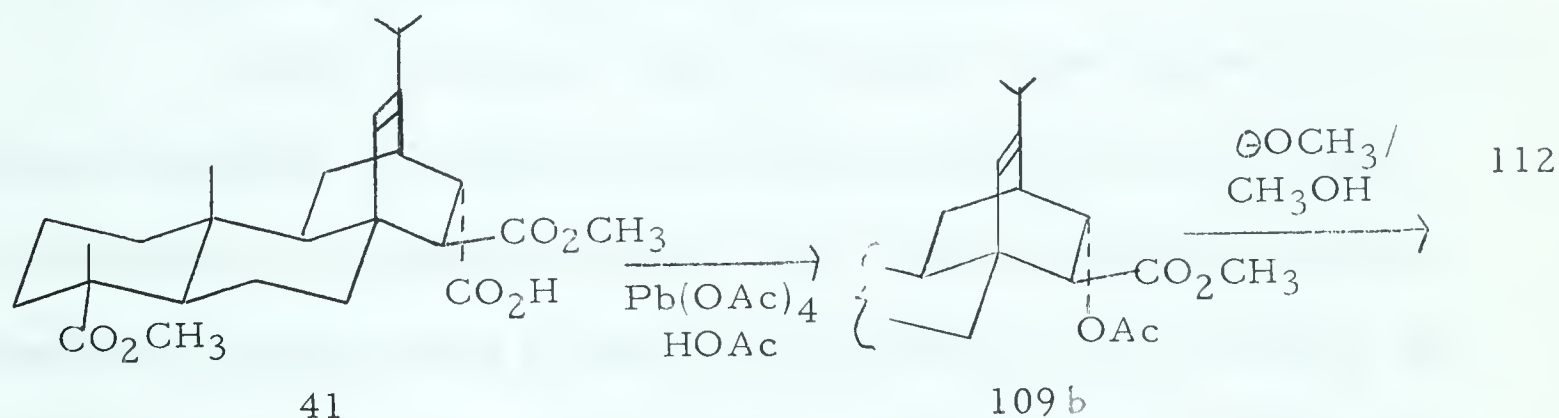
[†] Sample prepared in these laboratories by P. Deshpande.

orientation it lies outside the shielding cone of the double bond and is consequently unaffected. The observed τ values for compounds 112, 113 and 114 (6.40 τ , 6.38 τ and 6.42 τ , respectively) reflect this shielding effect and therefore must be endo to the double bond. In agreement with this conclusion is the reported n.m.r. spectrum of the C-22 exo dimethyl ester 115 which shows carbomethoxyl signals at 6.32 τ (C-1 ester) and 6.35 τ (C-22 ester)⁵¹.



Further evidence for the location of the ketone function at C-21 in the keto diester 113 was obtained from the ultraviolet and RD data. Thus the carbonyl group was found to possess an enhanced $n \rightarrow \pi^*$ absorption ($\lambda_{\max}$ 296 ($\epsilon=139$)) and a strongly negative Cotton effect curve with a trough at 317 $m\mu$ ($M = -23,400$). As has been discussed earlier (see page 92), these spectral properties are characteristics of a bicyclo (2.2.2) octeneone system. The C-21 carbonyl group was identified by the negative sign of the Cotton effect curve since this requires the presence of the chromophoric unit A (page 93) where the double bond in this case is readily located between carbons 7 and 8 by the 3-proton n.m.r. signal at 9.32 τ and a 1-proton peak at 4.29 τ due to the olefinic hydrogen at C-8.

Evidence for the location of a hydroxyl group at C-21 in the hydroxy diester 112 was obtained in the following manner. Decarboxylation of the monoacid dimethyl ester 41 (prepared by partial saponification of the cis trimethyl ester 34) with lead tetraacetate in acetic acid gave an oily mixture of products from which two oily acetates were isolated after extensive chromatographic purification. The major component was assigned the unrearranged structure 109b on the basis of n.m.r. signals at 9.38τ (3H), 8.00τ (3H), 5.55τ (1H, broad) and 4.66τ (1H). Zemplin methanolysis transformed 109b into the hydroxy dimethyl ester 112 identical by melting point, mixture melting point, and infrared spectral comparison.



The α orientation of the C-21 acetoxy and hydroxy substituents in these compounds, thus far assumed without proof, is based on three lines of evidence. First, from the decarboxylation of 41 there is an analogy with the decarboxylation of diacid 42 and 5-carboxybicyclo (2.2.2) octene in which the exo epimer predominates. Secondly, from the acetolysis of lactone II there is analogy with the acetolysis of tricyclo (2.2.2.0)^{2.6} octan-3-ol where only the exo epimer forms. Finally, from double irradiation experiments on the hydroxy diester 112 it was

possible to show that the C-21 proton was coupled to a proton at 7.94 τ (d., $J=5$ c.p.s.). This signal is assigned to the C-22 exo proton since the only other signal in the same region (at 7.44 τ) is better assigned to the C-6 proton because of its appearance as a broadened multiplet. On the basis of previous observations, which have shown that coupling of trans C-21 and C-22 hydrogens fall in the range of 4-6 c.p.s. while the eclipsed configuration is characterized by a 10-12 c.p.s. coupling, it is concluded that this coupling of 5 c.p.s. is only compatible with an exo orientated hydroxyl group.

Anisotropy Effects of the C-21 and C-8 Carbonyl Groups.

1. Shielding effect of the C-21 carbonyl group.

In the structural studies on lactone I and lactone II, two C-21 keto compounds, the keto lactone 94 and the keto diester 113, were synthesized. Comparison of the n.m.r. spectra with those of other members in each series revealed a deshielding of the C-8 proton and the C-12 methyl on introduction of the carbonyl function. The relevant n.m.r. signals are listed in Tables VIII and IX.

Examination of molecular models show that the C-8 proton and the C-12 angular methyl are suitably orientated for deshielding since they lie in the plane of the C-21 carbonyl group.

2. Shielding effect of the C-8 carbonyl function.

The two compounds synthesized which contain C-8 keto groups are the diketone 96 and the keto diester 105. Inspection of Table X shows that the C-12 methyl is shifted to higher field in these compounds

TABLE VIII

THE ANISOTROPY EFFECTS OF A C-21 CARBONYL GROUP - LACTONE I SERIES

	Lactone I	Hydroxy Lactone 93	Keto Lactone 94	Hydroxy Ketone 95	Thioketal 101	Diester 102
C-8 proton	5.21	5.24	4.97	--	5.30	5.29
C-12 methyl	9.06	9.06	8.98	8.98	9.07	9.03

TABLE IX

ANISOTROPY EFFECTS OF A C-21 CARBONYL GROUP - LACTONE II SERIES

	Acetoxy Acid 109a	Hydroxy Acid 111	Hydroxy Diester 112	Diester 114	Keto Diester 113
C-8 proton	4.63	4.63	4.64	4.64	4.29
C-12 methyl	9.38	9.37	9.37	9.38	9.32

TABLE X

ANISOTROPY EFFECTS OF A C-8 KETO GROUP

Lactone I series	Keto lactone 94	8.98 ;	hydroxy ketone 95	8.98 ;	diketone 96	9.17
Lactone II series	Lactone II	9.17 ;	hydroxy diester 104	9.03 ;	keto diester 105	9.27

a shielding effect which is not unexpected since these protons lie within the shielding cone of the carbonyl group.

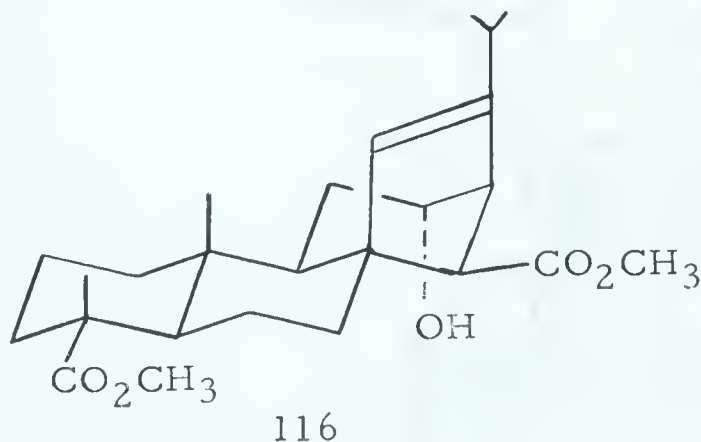
Lead Tetraacetate Decarboxylation of Monoacid (41)

Structure of the Minor Component.

In addition to the acetate 109b which has already been discussed, a small amount of a second oily acetate was isolated from the decarboxylation of the monoacid 41 with lead tetraacetate in acetic acid and assigned the structure 110b primarily on the basis of the following spectral data.

The presence of a secondary acetate was established by a three proton signal at 8.01τ and a broad one proton peak at 5.08τ . The olefinic proton was indicated by a signal at 4.87τ and the isopropyl group by a doublet at 8.90τ ($J=6.5$ c.p.s.). The C-12 angular methyl was found at 9.24τ and by analogy with isophyllocladene (C-12 methyl at 9.24τ) suggests a bicyclo (3.2.1) octene system for 110b.

Support for this structure was obtained by conversion of 110b to the hydroxy dimethyl ester 116, m.p. $101-103^{\circ}\text{C}$; mol. ion = 418) with sodium methoxide in methanol.



The hydroxyl group was identified by peaks in the infrared at

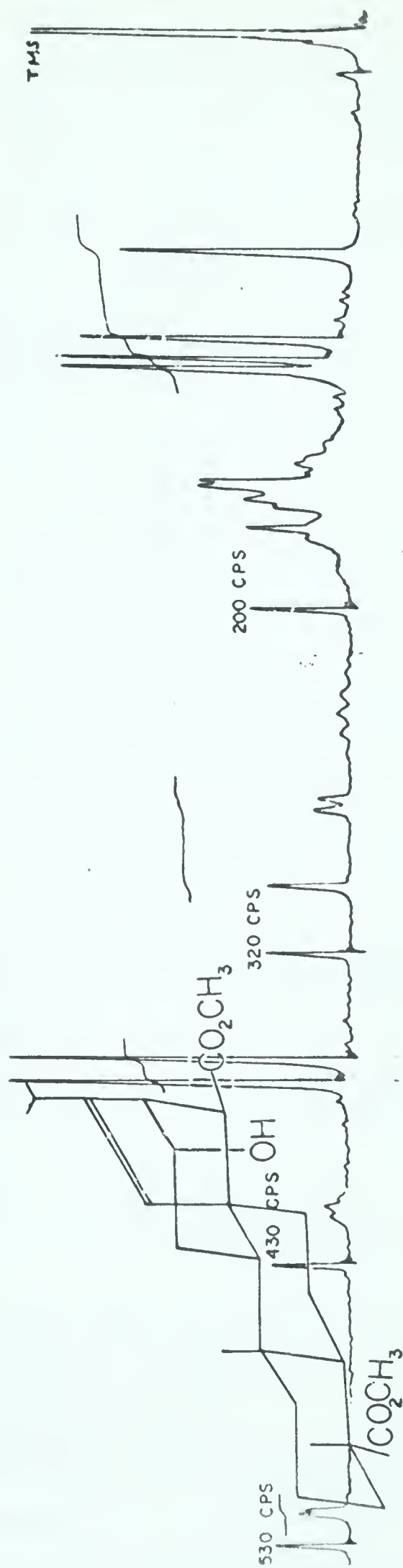
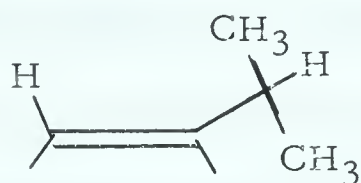


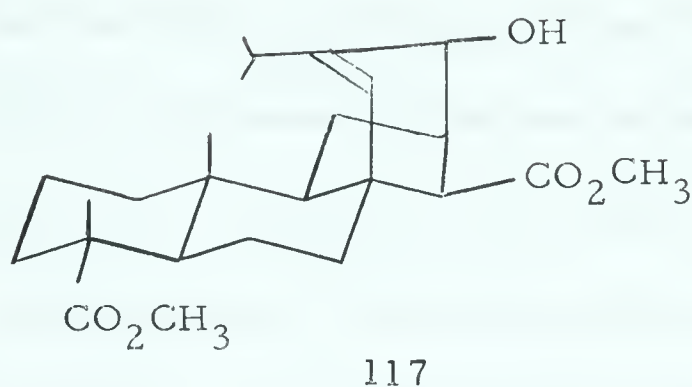
Figure 60. Nuclear magnetic resonance spectrum of the rearranged hydroxy dimethyl ester 116.
at 160 mc.

3610 cm^{-1} (sharp) and 3510 cm^{-1} (broad) and in the n.m.r. spectrum by a signal at 8.28 τ . Deuterium exchange removed this signal and shifted the infrared absorption down to 2670 cm^{-1} and 2600 cm^{-1} . Double irradiation experiments established a small coupling ($J=1.6$ c.p.s.) between the isopropyl methine and the olefinic proton at 4.82 τ . This is in the range expected for allylic coupling and consequently supports the part structure



contained in 116. In addition, double irradiation experiments showed that a broad 1 proton signal at 5.90 τ (CHOH) was coupled to a doublet at 7.32 τ ($J=4$ c.p.s.) and to a second proton at 8.40 τ , which from its chemical shift value, would appear to be a methylene hydrogen, presumably at C-5. The doublet at 7.32 τ is in the range expected of a tertiary allylic hydrogen and can therefore be assigned to the C-6 bridgehead methine. A third one proton signal, located at 7.03 τ and which is uncoupled, is assigned to the C-22 hydrogen. Only the rearranged structure 116 can meet the requirement that the hydroxyl bearing carbon be flanked by both a methine and a methylene proton, the unrearranged bicyclo (2.2.2) octene system and the alternative bicyclo (3.2.1) octene 117 (formed by migration of C-5 to C-21) being deficient in this respect.

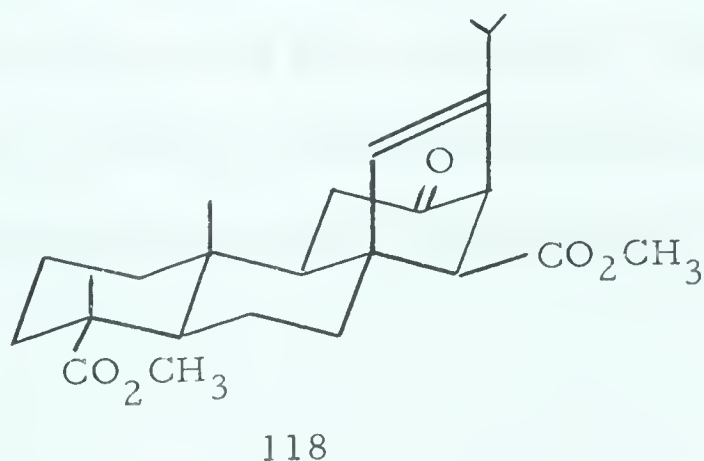
If it is assumed that the coupling between the C-5 hydrogen and the bridgehead methine is not significantly different from the couplings observed between a C-5 and a C-21 hydrogen in the bicyclo (2.2.2) octene



system (the dihedral angles are identical) then the observed coupling of 4 c.p.s. argues for an α oriented hydroxyl in the diester. This assignment is also in agreement with the expectation that the acetoxy group in the acetoxy dimethyl ester would be incorporated from the less hindered β side of the molecule.

The mass spectrum of 116 showed a surprisingly large peak at $m/e = 316$ (1.6% of total ionization) in view of the proposed bicyclo (3.2.1) octene system but it is nevertheless still well outside the range (3.6 - 6.6%) found in the bicyclo (2.2.2) octene series.

A small amount of the hydroxy diester 116 was oxidized with the Kiliani reagent and the RD curve of the oily two component (t.l.c. analysis) product obtained. The positive Cotton effect (extrema at 319 $m\mu$ ($M = +13,700$) and 280 $m\mu$ ($M = -9,320$) is that predicted by the generalized octant rule for the ketone 118.



It is interesting to note that when the monoacid was decarboxylated with lead tetraacetate in pyridine solution the oily product which was obtained following chromatography and vacuum distillation (see page 46) showed strong n.m.r. signals at 9.25 and 8.00 τ (2.4 and 2.2 H respectively, relative to the carbomethoxyl absorption) as well as a 1 proton peak at 4.81 τ . A comparison with the n.m.r. data of the rearranged acetate 110b suggests that this compound is probably a major constituent of the reaction product when the monoacid 41 is decarboxylated in pyridine solution. Presumably the low acetate concentration permits rearrangement of the intermediate to compete more favorably with acetate incorporation at C-21 than is the case in acetic acid solution.

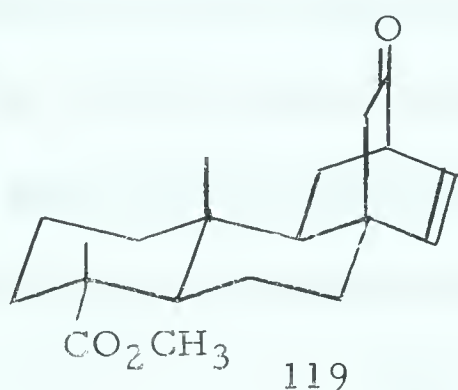
Oxidative Removal of the Isopropyl Group with Lead Tetraacetate.

In an early decarboxylation experiment the diacid 42 was treated with a two mole excess of lead tetraacetate in pyridine, no attempt being made to control the temperature of the exothermic reaction. Careful chromatography of the diene fraction on neutral alumina provided, besides the diene, a very low yield (ca. 0.2%) of a crystalline compound, melting point 169-71°C. A comparison of the spectral data (Table XI) with that reported for the keto olefin 119¹⁴¹, melting point 166-68°C suggested that the two compounds were identical. Compound 119 showed ultraviolet absorption at 239 $m\mu$ with an extinction coefficient of $\epsilon = 142$ in good agreement with that expected of the bicyclo (2.2.2) octenone system.

TABLE XI

Spectral Data fro the Keto Olefin 119.

	C-12 methyl	C-1 methyl	C-1 ester	C-21 H	C-22 H
N.M.R. Observed	9.07 τ	8.88(3) τ	6.37(3) τ	3.85-3.93 τ 2H; multiplet	
Reported	9.07 τ	8.88 τ		3.93 (d, $J=3$)	3.87 τ
I.R.					
Observed	1722 cm^{-1}	--	1240 cm^{-1}		
Reported	1724 cm^{-1}	1616 cm^{-1}	1248 cm^{-1}		

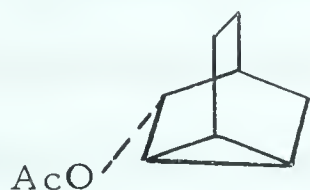


Lactone I and II - Mechanistic Speculations

As mentioned in the introduction the initial step in lead tetraacetate decarboxylation is the formation of a mixed ester $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{Pb}-(\text{OAc})_3$ which undergoes either a homolytic or heterolytic cleavage to generate the corresponding carboxylate radical or cation. In the absence of stabilization through an esterification process, carbon dioxide is lost and the corresponding carbon radical or carbonium ion results.

The importance of carbonium ions in the lead tetraacetate decarboxylation of norbornane-2-carboxylic acid¹²⁰ and 5-carboxybicyclo

(2.2.2) oct-2-ene¹³⁸ to the tricyclic acetates 97 and 106 in acetic acid supports the assumption that carbonium ions are involved in the system under discussion. In both these model compounds the orientation of the acetoxy group was that expected by approach from the less hindered side.

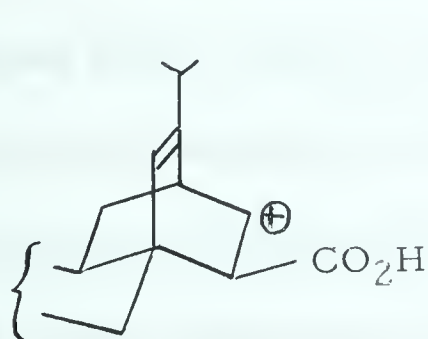


106

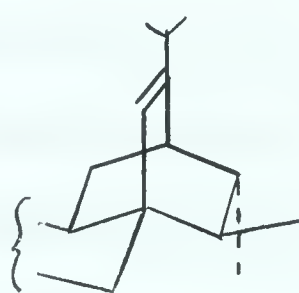


97

The decarboxylation of methyl fumaropimarate could thus lead to the carbonium ion $\ddagger$ A. Following the arguments of Le Bel and Haber¹³⁸, (A) can react in two ways (a) combination with acetate to give (B); (b) rearrangement to the non-classical carbonium ions (C), (D) and (F).



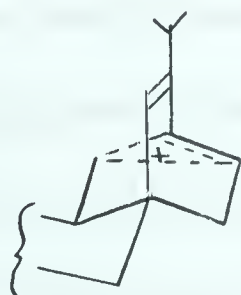
A



B



C



D



F

$\ddagger$ It is assumed that the cyclic lead ester is unimportant and that the less hindered C-21 carboxyl is involved in the ester exchange with lead tetraacetate.

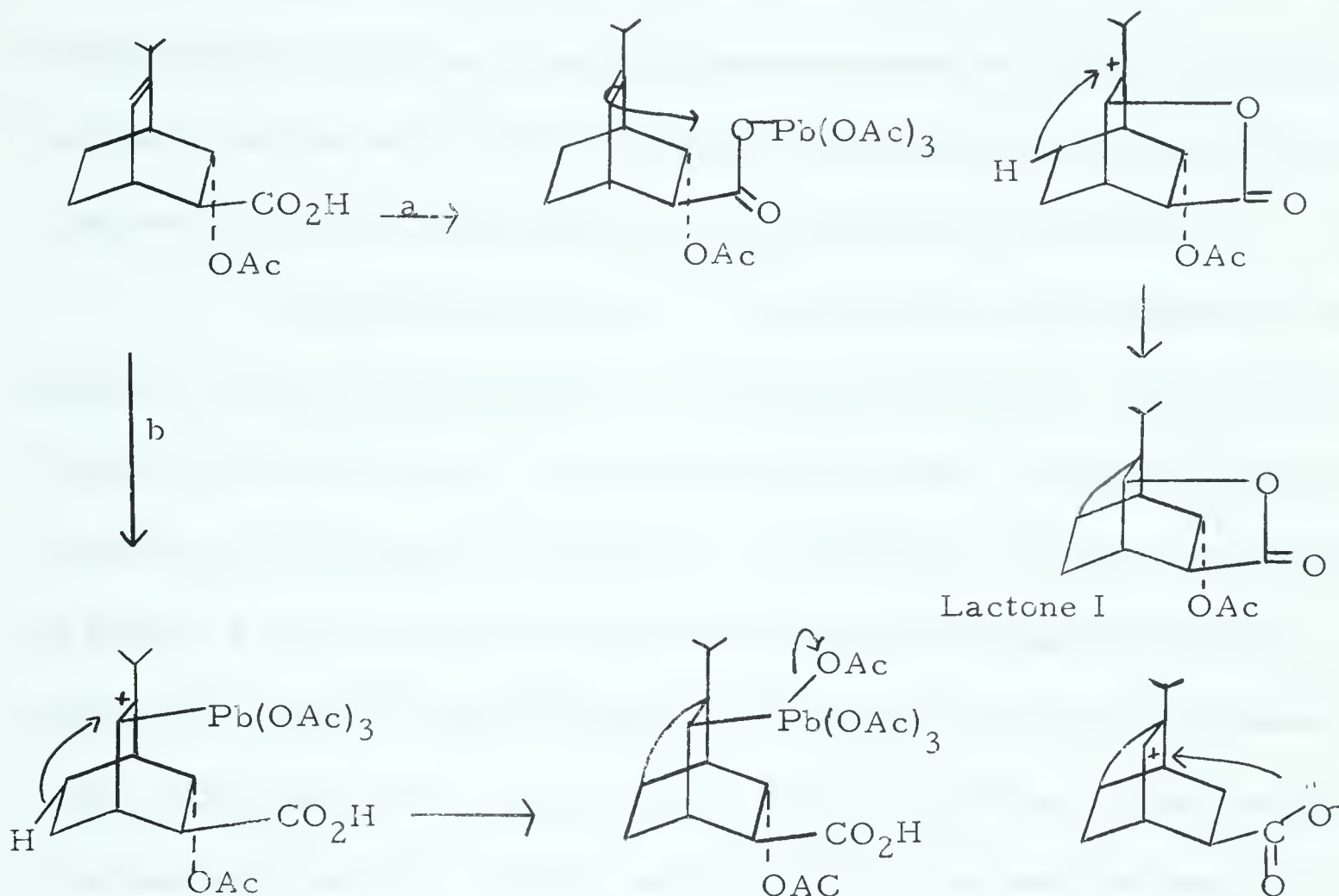
Intermediates analogous to the homoallylic ion (C) have been postulated in solvolytic studies on norbornene derivatives. In the ion (C) the product corresponding to the tricyclic acetate 106 would involve approach of the acetoxyl group at C-8 from above the C-21, C-22 ethano bridge. However, because of entropy factors this intermolecular reaction would not be expected to compete favourably with lactonization and it is probably for this reason that the C-8 acetoxyl derivative is not isolated.

Products deriving from acetate attack at C-5 of the rearranged ion (F) are not observed when C-22 is substituted by a free carboxyl group, possibly because rearrangement cannot compete with the lactonization process. However, when lactonization is blocked, as in the C-22 carbomethoxyl derivative 41, this migration is observed.

In neither the diacid 42 nor the monoacid 41 were compounds isolated which could be identified with the carbonium ion (D). This is in distinct contrast to the decarboxylation of 5-carboxybicyclo (2.2.2) oct-2-ene which produced axial bicyclo (3.2.1) oct-3-en-2-yl acetate but none of the axial bicyclo (3.2.1) oct-6-en-2-yl acetate. This apparent conflict can be removed by assuming a 1,3 diaxial interaction between the C-12 angular methyl and the C-7, C-8 ethylene bridge. Migration of C-7 to C-21 would tend to decrease this steric compression whereas migration of C-5 to C-21 would leave the interaction essentially unchanged.

The acetoxyl acid (B) although not isolated in the oxidation of diacid 42 with lead tetraacetate is assumed to be the precursor of lactone I into which it is converted by a second oxidation with lead tetraacetate.

Two plausible reaction pathways by which this may be effected are as follows:



The essential difference between these two alternatives is the initial point of attack by lead tetraacetate. Although neither can be ruled out it is felt that attack on the double bond is less favored for two reasons. First there is a greater degree of hinderance involved in the approach of Pb(OAc)₄ (or $\oplus\text{Pb}(\text{OAc})_3$) to the double bond than there is to the C-22 carboxyl group. Secondly, even in the absence of steric hinderance as, for example, in the bis decarboxylation product 99, oxidation of the C-21, C-22 double bond by lead tetraacetate is not observed. Insofar as the cyclopropane ring formation is concerned a distinction between these two possibilities is unimportant for they both lead to electrophilic attack on the

double bond, a necessary step for the cyclopropane ring closure reaction¹⁴⁴.

Reference has already been made in the introduction to the fact that the decarboxylation of methyl fumaropimarate with lead tetraacetate was also carried out in tetrahydrofuran-acetic acid and acetic acid solvents. The results of these experiments are summarized in Table XII.

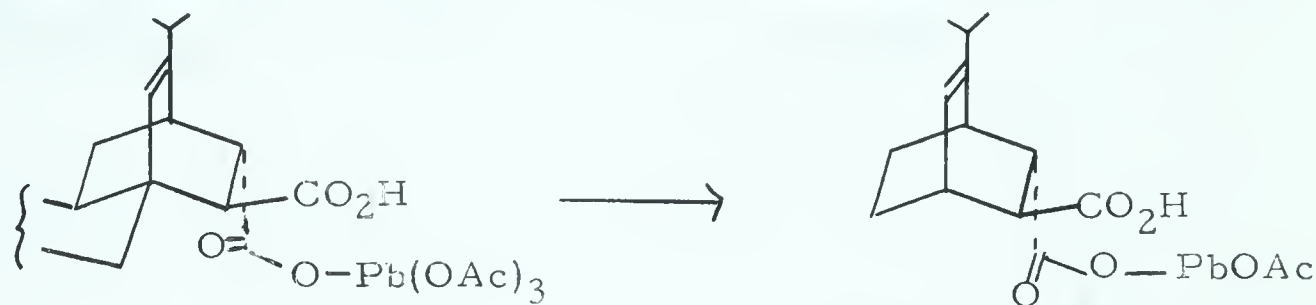
The significant feature of these results is the dependence of lactone I-lactone II distribution on acetate concentration. Thus, as the proportion of acetic acid in the solvent is increased, the yield of lactone I increases at the expense of lactone II. In pyridine solution, the proportion of lactone I was found to increase with the amount of lead tetraacetate employed. This is understandable in view of the previously discussed observation that lead tetraacetate is unstable in pyridine, decomposing in a matter of minutes at 65°C, and hence acts as a potential source of acetoxy residues.

TABLE XII

INFLUENCE OF SOLVENT AND $\text{Pb}(\text{OAc})_4$ CONCENTRATION ON LACTONE I - LACTONE II DISTRIBUTION

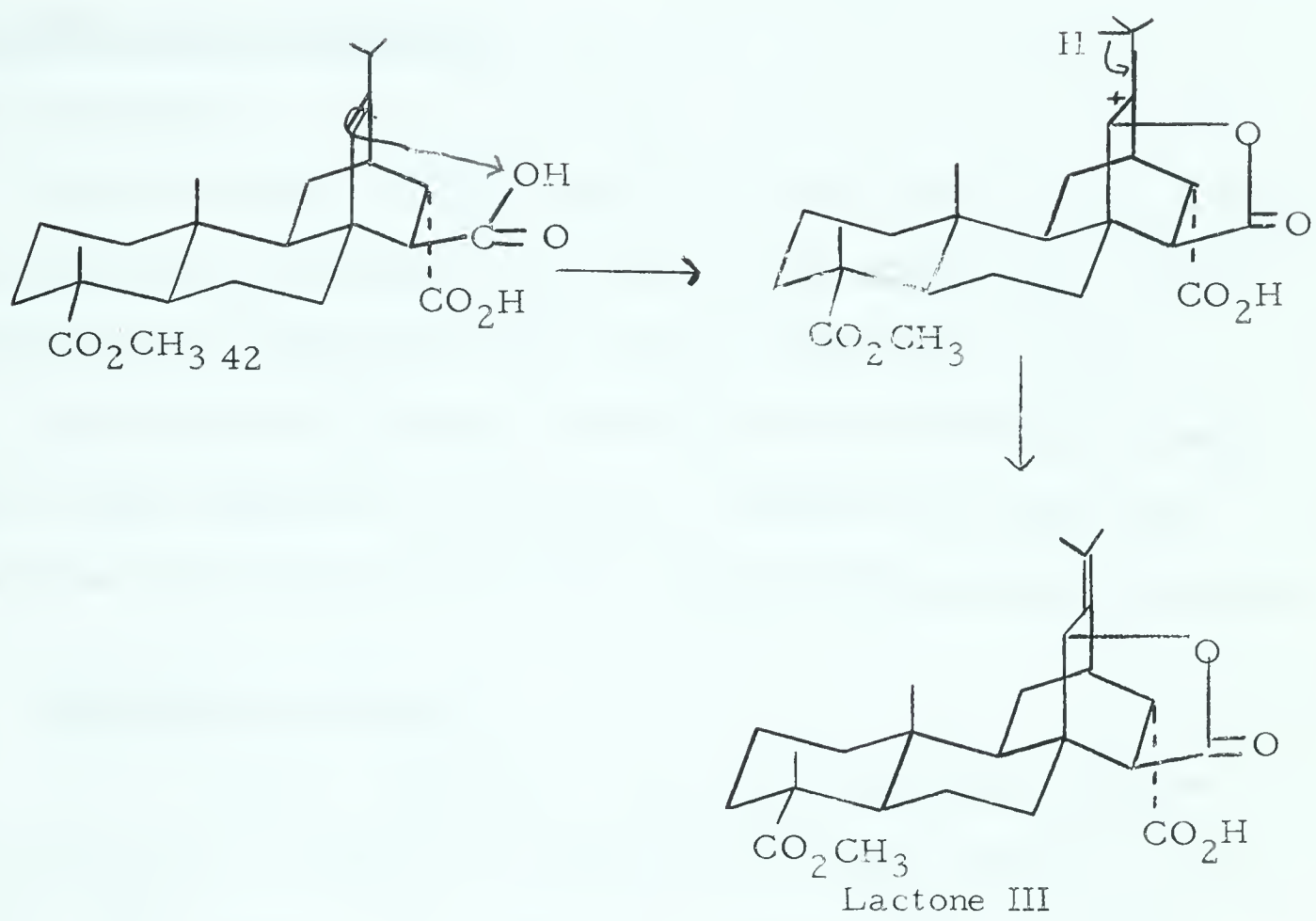
Exp.	Solvent	$\text{Pb}(\text{OAc})_4$ Diacid	Lactone I	Lactone II	Lactone III	Diene
1	pyridine	1.0	--	9%		(+)
2	pyridine	1.4	3%	7%	6%	10%
3	pyridine	2.1	8%	--		8%
4	THF/HOAc	2.0	4%	2%		9%
5	HOAc	2.7	11%	--		2%

The yields are calculated on the basis of moles of diacid 42 converted to isolated products. The generally poor yields experienced are attributed in part to the decomposition of a Pb IV ester of the diacid in such a manner as to give a divalent lead species still retaining the diacid molecule.



In all cases the diene arising from an oxidative bisdecarboxylation has been shown to be present among the products. The yields were in the order of 10% with either pyridine or tetrahydrofuran-acetic acid as solvent. No attempt was made to determine the extent of diene formation in acetic acid solvent. That it does form was shown by its isolation, albeit in trace amounts (1-2%), and characterization by infrared and n.m.r. analysis.

In terms of the proposed reaction scheme methyl fumaropimarate reacts with lead tetraacetate and the intermediate carbonium ion A then reacts either intramolecularly to give lactone II or is trapped by acetate to provide lactone I via the hypothetical acetoxy acid B. In experiments 3 and 5, where acetate concentration is high, the intermolecular reaction apparently occurs to the exclusion of the intramolecular cyclization. Formation of lactone III presumably involves an initial oxidation of the more hindered C-22 carboxyl group by lead tetraacetate.



EXPERIMENTAL

A. DECARBOXYLATION OF DIACID 42

a) In Pyridine

Diacid 42 (21 g., 0.049 moles) in pyridine (250 mls) was allowed to react with 31 g. of $\text{Pb}(\text{OAc})_4$ (0.07 moles, trace HOAc) at 30° . After fifteen minutes the temperature rose rapidly to 45°C and a gas was evolved. The solution was cooled to 30°C using an ice bath and allowed to stand at room temperature for 12 hours. Ethylene glycol was then added and the solvent evaporated on the steam bath under reduced pressure.

Isolation of products.

i. The neutral components: The residue obtained by evaporation of the solvent was washed with ether and the ether decanted. The process was then repeated three times. The combined ether solutions (500 mls) were extracted with distilled water, dilute aq. HCl and finally, to remove free carboxylic acids, with dilute aq. NaOH . Evaporation of the ether yielded 6 g. of neutral material which was chromatographed on 400 g. of silica gel. Fractions 2-4, eluted with 1.5 l of benzene, gave 1.7 g. (10% yield) of diene 40 as a colourless oil which showed one spot on two dimensional t.l.c. analysis. Calc. for $\text{C}_{23}\text{H}_{34}\text{O}_2$: C, 80.65; H, 10.00%. Found: C, 80.77; H, 9.80%. Infrared spectrum: $\sqrt{\text{max}}$ 3040(w), 1732(s), 1230 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.38(3H), 9.01(3H, $J=7\text{ cps}$), 8.99(3H, $J=7\text{ cps}$), 8.88 (3H), 7.20(2H, multiplet), 6.75(1H, multiplet), 6.38(3H), 4.59(1H, triplet), 4.05(1H, quartet), 3.84(1H, quartet). Mass spectrum: molecular ion at 342, 146 (4%), 133 (5.5%, base peak), 117(3.5%).

Fractions 7-8 (wt. 1.4 g., 7% yield; elution with 12% ether in benzene) afforded lactone II, (103) as needles m.p. 176-180°C after recrystallization from benzene-Skellysolve B, and ethyl acetate. Calc. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56%. Found: C, 74.48; H, 8.74; O, 16.56%. Infrared spectrum: $\nu_{\max}$ 1780(s), 1720(s), 1385(m), 1364(m), 1230(s). Nuclear magnetic resonance spectrum: τ 9.25(3H, $J=7.5$ cps), 9.17(3H), 8.96(3H, $J=7.5$ cps), 8.86(3H), 7.61(1H), 6.33(3H), 5.30(1H).

Fractions 10-12 (0.6 g., 3% yield, elution with 12% ether in benzene) afforded lactone I, (98) which was recrystallized from benzene-Skellysolve and methanol to give needles m.p. 194-195°C. Calc. for $C_{26}H_{36}O_6$: C, 70.25; H, 8.16; O, 21.60%. Found: C, 70.35; H, 7.88; O, 21.58%. Infrared spectrum: $\nu_{\max}$ 1784(s), 1740(s), 1722(s), 1386(m), 1368(m), 1242(s). Nuclear magnetic resonance spectrum: τ 9.15(3H, $J=7$ cps), 9.05(3H), 8.93(3H, $J=7$ cps), 8.79(3H), 8.00(1H), 7.90(3H), 7.78(1H), 6.31(3H), 5.19(1H), 4.83(1H, $J=5$ cps). Molecular weight determination (Rast) = 480. Lactone I gave a negative test with tetranitromethane.

ii. Acidic components. The carboxylic acids were present both in the free form and as the corresponding lead salts. The former were taken up in the ether washes as mentioned in part (i) and could be recovered from the basic extracts by acidification with dilute aqueous HCl.

The residual lead salts were dissolved in acetic acid and acidified with anhydrous HCl. The precipitated lead chloride was removed by filtration and the filtrate concentrated on the steam bath under reduced pressure. Benzene was added to the partially crystalline residue

and the insoluble portion (0.7 g.) collected by filtration. The I.R. and m.p. (276-279°) identified it as unreacted diacid 42. The benzene filtrate was concentrated, combined with the aq. sodium hydroxide-extracted acids of part (i) (total wt. = 12 g.) and chromatographed on 700 g. of silica gel. Elution with benzene (eight fractions; total volume 2.5 l.) provided only trace amounts of unidentified material. Elution with 25% ether in benzene (fractions 9-11; 400 mls) provided 0.75 g. of impure monoacid 41. Recrystallization from benzene-Skellysolve B and methanol gave the pure sample m.p. 179-182°C, I.R. superimposable on that of authentic material. The monoacid is probably present as an impurity in the starting material which had been prepared by saponification of the cis trimethyl ester 34. Continued elution with 25% ether in benzene (fractions 17-27; 1.0 l.) provided lactone III, 92a (1.4 g., 6% yield), m.p. 189-90° after three recrystallizations from benzene. Calc. for $C_{25}H_{34}O_6 \cdot \frac{1}{2}C_6H_6$: C, 71.60; H, 7.95; O, 20.44; OCH_3 , 6.61%. Found: C, 71.21; H, 7.95; O, 20.60; OCH_3 , 6.75%. Infrared spectrum: $\sqrt{\text{CHCl}_3}_{\text{max}}$, 1771(s), 1725(s), 1717(s), 1675 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.29(3H), 8.84(3H), 8.20(6H), 7.28(2H), 6.72(1H, broad), 6.33(3H), 4.97(1H), 2.61(3H, benzene), -0.75(1H).

The corresponding dimethyl ester 92b was prepared by reaction with ethereal diazomethane, melting point (after two recrystallizations from methanol) 180-181°C. Calc. for $C_{26}H_{36}O_6$: C, 70.25; H, 8.18; O, 21.59; OCH_3 , 13.96%. Found: C, 70.10; H, 8.38; O, 21.51; OCH_3 , 14.48%. Infrared spectrum: $\sqrt{\text{CHCl}_3}_{\text{max}}$, 1770(s), 1733(s), 1725(s), 1674 (w). Nuclear magnetic resonance spectrum: τ 9.30(3H), 8.85(3H), 8.23(6H), 7.31(2H), 6.82(1H), 6.36(3H), 6.28(3H), 5.02(1H), R.D. (in methanol) plain dispersion curve $[\alpha]_D^{-98^\circ}$, $[\alpha]_{500}^{-110^\circ}$, $[\alpha]_{400}^{-228^\circ}$

$[\alpha]_{350}^{25} -364, [\alpha]_{300}^{25} -702, [\alpha]_{280}^{25} -998, [\alpha]_{250}^{25} -2020.$

From the final fractions (30-31) from the chromatography (0.4 l of 25% ether in benzene) 0.2 g. of diacid 42 was isolated (m.p. 262-275°C; infrared spectrum identical with that of an authentic sample).

b) Decarboxylation of diacid 42 with lead tetraacetate in pyridine - a modified procedure for the preparation of lactone II.

Diacid 42 (18 g., 0.043 moles) was dissolved in 150 mls of pyridine (Karl Fisher reagent) and the solution cooled to 5°. Lead tetraacetate (18 g., 0.04 moles) was then added and the solution was stirred at 5° for 30 minutes and then at room temperature for twelve hours and finally on the steam bath for 45 minutes. The reaction mixture was then diluted with water and extracted with benzene. The combined benzene extracts were washed once with dilute aqueous HCl, then with distilled water and evaporated. The residue was filtered through acid washed alumina (60 g. elution with benzene and 20% ether in benzene) redissolved in benzene, extracted with 10% NaOH, washed with distilled water and concentrated. Two recrystallizations from benzene-Skellysolve gave 1.4 g. of lactone II (9% yield), m.p. 176-180°C.

c) Decarboxylation of diacid 42 with a large excess of lead tetraacetate in pyridine - isolation of the unsaturated ketone 117.

Diacid 42 (40 g., 0.09 moles) was dissolved in 250 mls of pyridine at room temperature and lead tetraacetate (82 g., 0.185 moles) was added. After 15 minutes a vigorous evolution of gas occurred accompanied by a rapid rise in the reaction temperature to 60°C. After one hour the solution was diluted with 350 mls of pyridine, 46 g. (0.10 moles) of Pb(OAc)₄ was added and stirring continued at room temperature

for 12 hours. Ethylene glycol was then added and the pyridine removed under reduced pressure. The residue was dissolved in benzene, washed with distilled water and chromatographed on 2.0 kg. of silica gel. Fractions 3-5 (2.0 l of benzene) provided 2.5 g. of oily bisdecarboxylated product (as judged by infrared analysis; 8% yield). Later fractions (12% ether in benzene) yielded oils from which lactone I (3.0 g., 8% yield) was obtained by a second chromatography (neutral alumina; act. III; elution with benzene) followed by recrystallization from benzene-pentane (m.p. 194-195°C, superimposable I.R.). Fractions 3-5 were filtered through 60 g. of neutral alumina (benzene-Skellysolve (1:1) to remove the yellow colouration and 0.4 g. of the colourless oil thus obtained carefully chromatographed on 15 g. of neutral alumina (activity 1-2). Elution with benzene-Skellysolve and benzene yielded only oily residues. Elution with 5% ether in benzene (0.26l) provided the ketone 117 (50 mgs). Infrared spectrum: $\checkmark_{\max}$ 3055(w), 3035(w), 1720(s), 1660(w), 1414(s). Nuclear magnetic resonance spectrum: (CCl₄) τ 9.07(3H), 8.88(3H), 6.37(3H), 3.85-3.93(2H). Three recrystallizations from methanol provided 4 mgs. of needles, m.p. 169-171°C, U.V. spectrum, $\lambda_{\max}^{\text{EtOH}}$, 293 *mμ* (ϵ = 142). Recovery of the U.V. sample, filtration and recrystallization from methanol provided the analytical sample C, 73.97; H, 8.22%. C₂₀H₃₈O₃ requires C, 75.91; H, 8.91%.

B. Decarboxylation of diacid 42 with lead tetraacetate in tetrahydrofuran-acetic acid solvent.

12.0 g. of Pb(OAc)₄ (27 mmoles) was suspended in 150 mls of T.H.F. containing 25 mls of acetic acid. Solution was effected during the subsequent addition of 11.5 g. (27 mmoles) of diacid 42. In the first

30 minutes of the reaction the temperature rose from 29°C to 32°C. After one hour an additional 11 g. of $\text{Pb}(\text{OAc})_4$ (25 mmoles) was added and stirring continued for $1\frac{1}{2}$ hours. During this time extensive precipitation (of $\text{Pb}(\text{OAc})_2$?) occurred. Unreacted $\text{Pb}(\text{OAc})_4$ was then destroyed by stirring with 5 mls of ethylene glycol for 15 minutes. The crude reaction product (6.2 g.) was obtained by diluting the solution with water, extracting twice with benzene, washing the combined benzene extracts with dilute aq. NaOH followed by distilled water and removal of the benzene under reduced pressure.

Chromatography on 180 g. of Harshaw alumina (basic to litmus) gave, in the first four fractions (0.4 l benzene), 0.6 g. of diene (9% yield) identified by infrared and n.m.r. analysis. Fractions 6-10 (0.4 l benzene) provided 0.20 g. of lactone II (2% yield), m.p. 172-182°C after two recrystallizations from benzene-Skellysolve. Fractions 12-14 (0.3 l benzene and 10% ether in benzene) provided oils which could not be recrystallized. Fractions 15-21 (1.0 l of 10% ether in benzene), 22-24 (0.4 l of 25% ether in benzene) and 25-26 (0.5 l of 50% ether in benzene) provided 0.50 g. (4% yield) of lactone I identified by m.p. and infrared comparison.

C. Decarboxylation of diacid 42 with lead tetraacetate in acetic acid.

Preparation of lactone I (98).

The diacid 42 (10 g., 0.023 moles) was suspended in 100 mls of hot acetic acid containing 2 mls of acetic anhydride and 12 g. (0.027 moles of $\text{Pb}(\text{OAc})_4$). The reaction mixture was kept at 90° for 10 minutes with very little evidence of reaction. The addition of anhydrous sodium

acetate (3.0 g., 0.037 moles) resulted in an immediate evolution of gas and dissolution of suspended diacid and $\text{Pb}(\text{OAc})_4$. After seven minutes an additional 16 g. (0.036 moles) of $\text{Pb}(\text{OAc})_4$ was added and heating continued for 30 minutes. Gas evolution was appreciably slower following the second addition of $\text{Pb}(\text{OAc})_4$. Water was then added and the solution extracted several times with chloroform. The combined chloroform extracts were washed once with water, dried over magnesium sulfate, filtered and evaporated. Chromatography on acid washed alumina (150 g.) and elution with 5% ether in benzene (0.5 l), 10% ether in benzene (0.5 l), and ether (0.5 l), gave crystalline material in all fractions. These were combined and recrystallized from benzene-Skellysolve to give 1.12 g. of lactone I (11% yield) identified by m.p. and infrared comparison.

D. Decarboxylation of diacid 42 with lead tetraacetate in dimethyl sulfoxide. Preparation of Lactone IV.

The diacid 42 (12 g. of 0.027 moles) was dissolved in 100 mls of D.M.S., 13 g. (0.029 moles) of $\text{Pb}(\text{OAc})_4$ added and the wine coloured solution allowed to stand at room temperature. After several minutes gas evolution commenced and the reaction temperature rose to 40°C . 8.0 g. (0.018 moles) of $\text{Pb}(\text{OAc})_4$ was introduced 30 minutes after the initial addition and the reaction mixture allowed to stand a further 1.5 hours. It was then diluted with benzene and washed, first with dilute aq. NaOH then with distilled water. Evaporation of the solvent left an oily residue (2.8 g.) which partially crystallized from Skellysolve but attempts to remove the crystals mechanically resulted only in their conversion to the gummy solid with which they had been deposited.

Chromatography on acid-washed alumina (60 g.) provided 0.25 g. of the diene 40 on elution with 1:1 benzene-Skellysolve (3% yield, identity established by I.R. comparison). Elution with benzene (0.4 l)

and ether-benzene (1:4; 0.2 l) resulted in the isolation of lactone IV, m.p. 175-185°C (0.27 g.) after one recrystallization from methanol. The analytical sample m.p. 185-186°C was prepared by recrystallization from methanol-ethyl acetate and benzene-Skellysolve. Calc. for $C_{24}H_{34}O_4Cl_2$ C, 63.01; H, 7.49; O, 13.99; Cl, 15.50%. Found: C, 62.96; H, 7.42; O, 16.41; Cl, 14.80%. Infrared spectrum: $\nu_{\max}$ 1786(s), 1720(s), 1232(s). Nuclear magnetic resonance spectrum: τ 8.98(3H), 8.95(3H, $J=7.5$ cps), 8.89(3H, $J=7.5$ cps), 8.76(3H), 7.70-8.00($\sim$ 5H), 7.5-7.7(4H), 6.33(3H), 5.63(1H, $J=1.6$ cps), 5.25(1H, d $J=4.2$ cps).

E. Reactions of the diene 40.

a) Thermal decomposition.

The diene 40 (100 mgs.) was heated under vacuum at 180°C for 25 minutes and the oily distillate (80 mgs.) examined by n.m.r. and ultraviolet spectroscopy. Nuclear magnetic resonance spectrum (CCl_4) τ 9.38 (0.4H); 8.98(2.1H); 8.81($J=7$ cps), 8.76; 6.34(3H), 5.0-5.3(1.1H); 3.0-3.3(2.5H). Ultraviolet spectrum: $\lambda_{\max}$ 254, 262, 270 and 274.

In another experiment the diene 40 was heated under vacuum at 100°C for 30 hours and the oily product submitted for n.m.r. analysis. Weak signals at τ 3 (1H), and 5 τ (0.5H) together with peaks at 8.76 and 8.82 τ indicated that some aromatization had occurred.

b) Hydrogenation of 40 to the dihydro derivative 91.

Diene (260 mg.) was dissolved in methanol (6 mls) containing 14 mgs of platinum oxide and hydrogenated at room temperature and atmospheric pressure for 22 hours. Removal of the catalyst and concentration of the filtrate yielded the oily dihydro derivative (220 mgs) in 90% yield. Infrared spectrum: $\nu_{\max}$ 1720(s), 1240 cm^{-1} (s). Nuclear magnetic

resonance spectrum (CCl_4): 9.42(3H), 9.02(6H, $J=8$ cps), 8.91(3H), 6.37(3H), 4.60(1H).

F. LACTONE I - STRUCTURAL INVESTIGATIONS

a) Zemplin Methanolysis of Lactone I

Lactone I (0.312 g., 0.7 mmoles) was dissolved in 10 mls of anhydrous methanol. Sodium metal (0.010 g., 0.44 mmoles) was added and the solution allowed to stand at room temperature for nine hours. Water (100 mls) was then added and the organic material collected in two methylene chloride washes. These were combined, dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization of the residue from benzene-Skellysolve B gave the hydroxy lactone 93 (0.245 g., m.p. 189-190°C) in 88% yield. Calc. for $\text{C}_{24}\text{H}_{34}\text{O}_5$: C, 71.61; H, 8.52; O, 19.87%. Found: C, 72.25; H, 8.31; O, 19.60%. Infrared spectrum: ν_{max} 3610(sharp), 3480(broad)(concentration dependent), 1782(s), 1729(s), 1240 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.15 (3H, $J=7$ cps), 9.06(3H), 8.94(3H, $J=6.5$), 8.80(3H), 7.83(2H), 7.22 (concentration dependent), 6.33(3H), 5.78(1H, triplet), 5.24(1H).

Acetylation of the hydroxy lactone 93

The hydroxy lactone (0.008 g.), was reacted with 0.8 mls of acetic anhydride in 1.0 mls of pyridine for two hours at room temperature. The solution was then diluted with benzene, washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The crystalline residue afforded 1.5 mgs of lactone I, m.p. 193-195°C, mixed m.p. 193-195°C. The infrared spectrum (semi-micro cell) was superimposable upon that of lactone I.

b) Oxidation of the hydroxy lactone 93 to the keto lactone 94

The hydroxy lactone (0.344 g., 0.86 mmoles) was dissolved in 25 mls of acetic acid containing 0.45 mls of Kiliani reagent (1.0 mmoles $K_2Cr_2O_7$). The solution was stirred at room temperature for 60 minutes then diluted with 100 mls of distilled water and extracted four times with benzene (total vol. = 200 ml). The combined benzene extracts were washed several times with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated to give a light coloured foam. One recrystallization from benzene-Skellysolve B gave 0.30 g. (88% yield) of the dimorphic keto lactone 94 as fine white needles, m.p. 179-180; 184-185°C. Calc. for $C_{24}H_{32}O_5$: C, 71.96; H, 8.07; O, 19.97%. Found: C, 71.80; H, 8.01; O, 20.18%. Infrared spectrum: $\sqrt{CHCl_3}_{max}$ 1790(s), 1725(s), 1715(s), 1245 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.11(3H, J=7), 8.98(3H), 8.88(3H, J=6.5), 8.78(3H), 7.94(2H), 7.25(1H), 6.35(3H), 4.97(1H). Ultraviolet spectrum: λ_{max} 286 ($\epsilon = 82$), 199 ($\epsilon = 2,400$). R.D. in methanol (c = 0.33). Positive Cotton effect curve $[\alpha]_{589} +92^\circ$
 $[\alpha]_{500} +210^\circ$ $[\alpha]_{400} +494^\circ$ $[\alpha]_{350} +930^\circ$ $[\alpha]_{318} +2060^\circ$ (inflection
 $[\alpha]_{308} +2370(max)$, $[\alpha]_{285} 0$ $[\alpha]_{270} -745$ $[\alpha]_{260} -550$

c) Conversion of the keto lactone 94 to the hydroxy ketone 95 with sodium methoxide.

Keto lactone 94 (0.30 g., 0.75 mmoles) was dissolved in 150 mls of anhydrous methanol to which had been added 2.1 g. of sodium metal (0.61 molar in methoxide ion) and the solution was refluxed eighteen hours protected from atmospheric moisture with a calcium sulfate drying tube. The solution was then concentrated, dilute aq. HCl added and extracted

three times with chloroform. The combined chloroform extract, after washing with water, was evaporated to give 0.29 g. of the crystalline hydroxy ketone 95 (quantitative conversion). Recrystallization from benzene and methanol provided the analytical sample, m.p. 228-229°C. Calc. for $C_{23}H_{34}O_4$: C, 73.74; H, 9.16; O, 17.09%. Found: C, 74.04; H, 8.93; O, 17.06%. Infrared spectrum: $\checkmark_{\max}^{CHCl_3}$ 3610(sharp), 3450(broad), 1727(s), 1687 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.05(3H, $J=8$), 8.98(3H), 8.92(3H, $J=7$ cps), 8.80(3H), 7.68(1H), 7.36(1H)(concentration dependent) 6.32(3H), 5.58(1H). Ultraviolet spectrum: $\lambda_{\max}$ 275 $m\mu$ ($\epsilon = 50$).

d) Oxidation of the hydroxy ketone 95 to the diketone 96.

The hydroxy ketone (0.089 g., 0.24 mmoles) was stirred at room temperature with 0.15 mls of Kiliani reagent (0.11 mmoles $K_2Cr_2O_7$) in 4 mls of acetic acid. After 60 minutes excess reagent was destroyed with methanol and the solvent evaporated. Water was added and the organic material extracted three times with chloroform (total vol. - 10 mls). The combined chloroform extracts were washed with distilled water and evaporated to yield the crystalline diketone 96, m.p. 178-179°C after recrystallization from 95% ethanol. Calc. for $C_{23}H_{32}O_4$: C, 74.15; H, 8.67; O, 17.18%. Found: C, 73.99; H, 8.74; O, 17.10%. Infrared spectrum: $\checkmark_{\max}$ 1742(sh), 1727(s), 1715(s), 1245(s). Nuclear magnetic resonance spectrum: τ 9.23; (3H, $J=7$ cps), 9.17(3H), 8.91(3H, $J=7$ cps), 8.86(3H), 7.92(2H), 7.67 and 7.75(3H), 6.36(3H). Ultraviolet spectrum: $\lambda_{\max}$ 273-87 $m\mu$ ($\epsilon = 90$), 202 $m\mu$ ($\epsilon = 6500$; CH_3OH). Mass spectrum: molecular ion at $m/e = 370 \pm 2$, 176(4.7%), 137(6.7%), 109(9.2%), base peak.

e) Conversion of the keto lactone 94 to the thioketal derivative 101

The keto lactone (0.20 g., 0.5 mmoles) was dissolved in 3.0 mls of freshly distilled boron trifluoride-etherate containing 0.53 g. (5.6 mmoles) of ethanedithiol and allowed to stand at room temperature for 45 minutes. Benzene (50 mls) was then added, the solution washed several times with distilled water, dried with anhydrous magnesium sulfate, filtered and evaporated. One crystallization of the solid residue from ethyl acetate gave 0.12 g. of crude thioketal, m.p. 225-236°C. Chromatography of the mother liquors on neutral alumina provided an additional 17 mgs of thioketal 101, m.p. 222-233°C (total yield = 58%). The analytical sample, m.p. 238-239°C, was prepared by recrystallization from ethyl acetate and then from benzene-Skellysolve B. Calc. for $C_{26}H_{36}O_4S_2$: C, 65.52; H, 7.62; S, 13.45%. Found: C, 65.57; H, 7.60; S, 13.61. Infrared spectrum: $\checkmark_{\max}^{CHCl_3}$ 1765(s), 1712(s), 1240 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.12(3H, J=7 cps), 9.07(3H), 8.89(3H, J=6 cps), 8.80(3H), 7.89(1H), 7.43(1H, J=3 cps), 6.6(4H, multiplet), 6.33(3H), 5.30(1H).

f) Desulfurization of the thioketal 101

The thioketal (.170 g., 0.36 mmoles), m.p. 232-237°C was refluxed with 4 g. of Raney nickel in 30 mls of acetone for 8.5 hours. The nickel was then filtered off, washed with acetone (75. mls) and the filtrate evaporated. The crude deoxy compound (0.113 g., 82% yield) crystallized on trituration with methanol (m.p. 118-128°C). Recrystallization from methanol provided the analytical sample, m.p. 135-137°C. Calc. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56%. Found: C, 74.75; H, 8.79; O, 16.97%. Infrared spectrum: $\checkmark_{\max}$ 1775(s), 1723(s), 1232 cm^{-1} (s).

Nuclear magnetic resonance spectrum: τ 9.14(3H, J-7 cps), 9.03(3H), 8.87(3H, J-7 cps), 8.81(3H), 6.36(3H), 5.29(1H).

g) Cleavage of the cyclopropane ring with *p*-toluenesulfonic acid:

Acetic acid solvent

Lactone I (0.24 g., .55 mmoles) was heated on the steam bath for 24 hours in 25 mls of acetic acid containing 150 mgs of *p*-toluenesulfonic acid. Water was then added to the solution and the organic precipitate taken up in methylene chloride, washed with water and evaporated. The residual oil showed three spots on t.l.c. (Al_2O_3 ; H_2SO_4 spray) and could not be induced to crystallize. Chromatography on neutral alumina (8 g.) provided the crystalline bicyclo (3.2.1) octene 99, eluted with ether-Skellysolve (1:1, 200 mls). Recrystallization from methanol and Skellysolve gave the analytical sample, m.p. 171-172°C. Calc. for $\text{C}_{24}\text{H}_{32}\text{O}_4$: C, 74.96; H, 8.40%. Found: C, 74.72; H, 8.20%. Infrared spectrum: $\checkmark_{\text{max}}$ 3042(w), 1765(s), 1720(s), 1630(w), 1235(s). Nuclear magnetic resonance spectrum: see Table VII page, 220. Elution with ether (100 mls) gave an oily mixture of 100 and a second component. The final fractions (elution with chloroform and 1:10 methanol-chloroform) contained the third component (10 mgs), m.p. 192-199°C after one recrystallization from Benzene-Skellysolve. Infrared spectrum: $\checkmark_{\text{max}}$ 3610(weak), 3480(broad), 1770(s), 1235(s).

The oily ether fractions were carefully rechromatographed on 5 g. of neutral alumina. Elution with ether-Skellysolve B (1:3) gave first a small amount of the diolefin 99, m.p. 169-172°C, followed by a series of oily fractions and then by the crystalline second component. Recrystallization from methanol and Skellysolve provided 4 mgs of plates, m.p.,

180–182°C. Infrared spectrum: $\checkmark_{\max}$ 1780(s), 1722(s), 1230 cm^{-1} (s).

Lactone I could be recovered unchanged after heating on the steam bath in acetic acid solution for 9.5 hours or by allowing it to stand 48 hours at room temperature in acetic acid–acetic anhydride (10:1) containing an equimolar amount of *p*-toluenesulfonic acid.

ii. Benzene solution

Lactone I (1.74 g., 3.92 mmoles) was refluxed on the steam bath with 0.500 g. of *p*-toluenesulfonic acid in 80 mls of benzene for 12 hours. The solution was then cooled and filtered through acid washed alumina (20 g., elution with 0.200 l of ether–benzene (1:20)). Evaporation of the eluent and recrystallization from Skellysolve B provided 1.30 g. (86% yield) of the diolefin 99, m.p. 167–170°C. An additional 45 mgs of product, m.p. 148–170°C was obtained from the mother liquors (total yield = 90%).

h) Hydrogenation of the diolefin 99

The diolefin 99 (0.461 g., 1.20 mmoles) was dissolved in 50 mls of ethyl acetate containing 55 mgs of platinum oxide and hydrogenated at atmospheric pressure. Hydrogen uptake (30 mls, 1.34 mmoles) was complete within 30 minutes. The crude bicyclo (3.2.1) octane 100, m.p. 174–182°C (0.465 g., quantitative yield) was obtained on filtration and evaporation of the filtrate. Recrystallization from ethyl acetate and benzene–Skellysolve B provided the analytical sample, m.p. 184–185.5°C. Calc. for $\text{C}_{24}\text{H}_{34}\text{O}_4$: C, 74.56; H, 8.89; O, 16.56%. Found: C, 74.62; H, 8.92; O, 16.41%. Infrared spectrum: $\checkmark_{\max}$ 1765(s), 1722(s), 1632(w), 1240 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.29(3H), 8.82(3H), 8.32(3H), 8.26(3H), 6.32(3H), 5.00(1H).

G. LACTONE II - STRUCTURAL STUDIESa) Hydrolysis of the γ lactone.

Sodium metal (0.109 g., 4.7 mmoles) was dissolved in 2.0 mls of anhydrous methanol and added to 6 mls of dimethyl sulfoxide (filtered through a column of molecular sieves followed by distillation through a vigreux column packed with glass helicies). Lactone II (0.210 g., 0.544 mmoles) was then introduced, solution effected by warming on the steam bath, and the reaction mixture allowed to stand at room temperature for seven days. At the end of this period, benzene was added, the solution washed several times with water, dried with anhydrous magnesium sulfate, filtered and evaporated. The trace of oil thus obtained was not investigated. Acidification of the aqueous extracts with conc. HCl precipitated the crude hydroxy acid. This was dissolved in chloroform, washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The crystalline residue (0.20 g., 91% yield) was recrystallized several times from ethyl acetate-methanol to give the pure hydroxy acid 104a, m.p. 212-215°C. Infrared spectrum: $\nu_{\max}$ 3480(broad), 3300-2400(broad), 1710 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.28(3H, d, $J=7$ cps), 9.04(3H), 8.97(3H), 8.87(3H), 7.48(1H), 6.38(3H), 5.72(1H).

Esterification with diazomethane provided the corresponding dimethyl ester 104b. Recrystallization from methanol and benzene-Skellysolve B provided the analytical sample, m.p. 140-141°C. Calc. for $\text{C}_{25}\text{H}_{38}\text{O}_5$: C, 71.73; H, 9.15; O, 19.11%. Found; C, 71.84; H, 9.06; O, 19.50%. Infrared spectrum: $\nu_{\max}$ 3460(broad), 1715(s), 1230 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.27(3H, $J=7$ cps), 9.03(3H), 8.95(3H, $J=7$ cps), 8.89(3H), 7.60(1H), 6.49(1H, $J=12$ cps), 6.41(3H), 6.35(3H), 6.00(1H, $J=12$ cps).

The hydroxy diester 104b was also obtained in poorer yield and less pure form by the following procedure.

Sodium metal (0.090 g., 0.39 moles) was dissolved in 8 mls of anhydrous methanol. Lactone II (0.100 g., 0.26 mmoles) in 5 mls of tetrahydrofuran (distilled from LiAlH_4) was then introduced and the solution allowed to stand at room temperature for nine days. Benzene was then added, the solution washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated to give a colourless oil from which the hydroxy diester slowly crystallized. Several recrystallizations from methanol and Skellysolve provided the purified sample of 104b, m.p. $138-141^\circ\text{C}$, undepressed on admixture with the sample prepared from 104a. The I.R. spectrum indicated a small amount of lactonic contaminant.

b) Oxidation of the diester 104b to the keto diester 105.

The hydroxy diester (0.095 g., 0.23 mmoles) was dissolved in 5 mls of acetic acid. Kiliani reagent (0.15 mls, 0.11 mmoles $\text{K}_2\text{Cr}_2\text{O}_7$) was added and the solution stirred at room temperature for one hour, then with 0.5 mls of methanol for five minutes to destroy excess reagent. The organic material was precipitated with water and taken up in chloroform (4 washes, total vol. 50 mls). The combined chloroform solutions were washed with distilled water, dried over anhydrous magnesium sulfate, filtered, and evaporated. Recrystallization of the solid residue from Skellysolve and then methanol provided the keto diester 105, m.p. $122-123^\circ\text{C}$. Infrared spectrum: $\checkmark_{\text{max}}$ 1729(sh), 1718(s), 1240(m), 1220 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.27(3H), 9.06(3H, $J=7$ cps), 8.96(3H, $J=7$ cps), 8.88(3H), 7.80-7.92(1H, multiplet),

7.28(1H), 6.37(6H). Ultraviolet spectrum: $\lambda_{\text{max}}^{\text{EtOH}}$ 288 m μ ($\epsilon = 70$),
 $\lambda_{\text{max}}^{\text{isooctane}}$ 202 m μ ($\epsilon = 4,000$). R.D. in methanol ($c = 0.204$) positive
 Cotton effect curve. $[\alpha]_{\text{D}} -39^{\circ}$ $[\alpha]_{500} -49^{\circ}$ $[\alpha]_{400} +34^{\circ}$ $[\alpha]_{350} +274^{\circ}$
 $[\alpha]_{303} -2580^{\circ}(\text{max})$ $[\alpha]_{280}^0$ $[\alpha]_{280} -2115^{\circ}$ $[\alpha]_{268} -3320^{\circ}(\text{min})$
 $[\alpha]_{250} -2520^{\circ}$.

Attempted deuterium exchange of the keto diester 105.

Sodium metal (25 mgs, 1.1 mmoles) was dissolved in 5 mls of CH_3OD . 28 mgs of the keto diester (0.067 mmoles) was added, the solution stoppered and allowed to stand at room temperature for six days. Ether was then introduced, the solution washed several times with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated, (21 mgs, m.p. 110-123°C after one recrystallization from Skellysolve). The n.m.r. sample (m.p. 121-123°C) provided a spectrum identical with that of starting material.

c) Solvolysis of lactone II with acetic acid - Isolation of the hydroxy acid 111.

Lactone II (1.26 g., 3.26 mmoles) was heated on the steam bath for twenty minutes in 50 mls of acetic acid. Water was then added and the solution washed four times with benzene (combined vol. = 200 mls). Evaporation provided a quantitative yield of oily solvolysis product. Infrared spectrum: $\checkmark_{\text{max}}$ 3300-2500(broad), 1715(s), 1695(s), 1225 cm^{-1} (s). Nuclear magnetic resonance spectrum: γ 9.38(2.4H), 8.95(J=6.5 cps), 8.89, 8.00(3H), 7.25(1H, broad); 6.40(3H), 5.50(0.8H, broad), 4.63(0.8H).

Attempts to crystallize the free acid or the derived

cyclohexylamine salt from a variety of solvents were unsuccessful. The reaction product was therefore deacetylated by allowing it to stand for 10 hours in 25 mls of methanol containing 4.3 mmoles of sodium methoxide. Addition of dil. HCl, extraction with benzene and evaporation of the solvent provided an oil from which the hydroxy acid 111, m.p. 114-154°C (0.55 g., 42% yield) could be obtained by addition of Skellysolve and seeding. Further recrystallization from methanol-water and benzene-Skellysolve raised the melting point to 157-161°C. Infrared spectrum: $\checkmark_{\text{max}}^{\text{CHCl}_3}$ 3610(sharp), 3510(broad), 3350-2400(broad), 1710(s), 1250 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.37(3H), 8.97(3H, $J=7$ cps), 8.86(3H), 6.34(3H), 6.23(1H), 4.63(1H).

The crystalline hydroxy acid used as seed in the above experiment was obtained in the following manner. Lactone II (0.700 g., 1.81 mmoles) was heated on the steam bath for nine hours in 50 mls of acetic acid. Water was then added and the products extracted with benzene. After washing several times with water the solvent was evaporated and the oily residue chromatographed on 50 g., of silica gel. The early fractions (1:1 benzene-Skellysolve (0.51)); benzene (0.7 l); 1:100 ether-benzene (0.4 l) and 1:20 ether-benzene(0.5 l)) contained two uncharacterized minor components. Elution with 1:10 ether-benzene (0.5 l) and 1:4 ether-benzene provided the two major components of nearly identical polarity as shown by t.l.c. analysis (silica gel, H_2SO_4 spray). These were converted to the oily hydroxy acid mixture (three components by t.l.c. analysis) as described above. The cyclohexylamine salt crystallized from benzene-Skellysolve solution as an amorphous white solid. The carboxylic acid was recovered by shaking a benzene solution of the salt with dil. aqueous HCl followed by evaporation of the solvent. Crystallization of the resulting

oil was induced by trituration with methanol. The purified sample melted at 161-162°C when recrystallized from benzene-Skellysolve but showed dimorphic properties when recrystallized from methanol (m.p. 105-125; 159-168°C).

d) Preparation of the hydroxy dimethyl ester 112.

i. From lactone II

The hydroxy acid 111 (.175 g. 0.434 mmoles) was dissolved in methanol and esterified with diazomethane. Recrystallization from methanol-water and benzene-Skellysolve yielded 0.140 g. (77% yield) of the hydroxy diester, m.p. 134-136°C. The analytical sample melted at 135-136°C. Calc. for $C_{25}H_{38}O_5$: C, 71.73, H, 9.15%. Found: C, 71.56; H, 9.20%. Infrared spectrum: $\checkmark_{\max}$ 3610(sharp), 3510(broad), 1715(s), 1230 cm^{-1} (m). Nuclear magnetic resonance spectrum: γ 9.37(3H), 8.95(6H, $J=7.5$ cps), 8.87(3H), 7.94(1H, $J=4$ cps), 7.5-7.9(2H, complex), 7.44(1H, broad singlet), 6.40(3H), 6.31(3H), 6.24(1H, broad triplet), 4.64(1H). Mass spectrum: 316(6.2%, base peak), 146(5%), 133(3.4%), 121(3.9%), 101(2.7%).

In earlier experiments the dimethyl ester 112 was obtained by treating the oily solvolysis mixture with sodium methoxide in methanol followed by esterification with diazomethane and chromatography on neutral alumina (elution with 1:1 ether-benzene), or alternatively, by esterification, then Zemplin methanolysis and chromatography. In all cases the diesters were identical by m.p., mm.p., and infrared comparison.

ii. Decarboxylation of mono acid 41 as an alternative route to the hydroxy diester 112.

The monoacid 41 (5.0 g., 11.2 mmoles) was dissolved in 50 mls.

of acetic acid containing 2.0 g., of sodium acetate. Lead tetraacetate (10.0 g., 26.0 mmoles) was added to the solution which was then heated at 90°C for 35 minutes. Water was then introduced and the organic material taken up in benzene. The combined benzene washes (400 mls) were dried over anhydrous magnesium sulfate, filtered and evaporated. The oily residue was subjected to the following chromatographic purification procedure.

The initial chromatography was carried out on 100 g. of acid washed alumina. Fractions 1-2 (200 mls of 1:1 benzene-Skellysolve) yielded an oily residue (0.20 g.) consisting primarily of the minor acetoxy component 110b (n.m.r. analysis). Subsequent fractions (elution with benzene, ether and chloroform) were combined and rechromatographed on 75 g. of acid washed alumina (chromatography #2). Elution with Skellysolve (0.30 l) and benzene-Skellysolve (1:1, 1.5 l) provided only traces of uncharacterized oil. Elution with 1:1 benzene-Skellysolve (1.5 l) yielded oils rich in the major acetoxy component 109b. The ether and chloroform fractions provided a crystalline mixture of the hydroxy esters 112 and 116 which on recrystallization from Skellysolve gave mixed crystals, m.p. 116-120°C. Infrared spectrum: $\nu_{\max}$ 3610(sharp); 3510(broad); 1715(s); 1230 cm^{-1} (s).

Final purification of the minor component 110b was achieved by chromatographing fractions 1-2 of chromatography #1 on neutral alumina (8 g., elution with 1:1 benzene-Skellysolve). Infrared spectrum: $\nu_{\max}$ 1719(s), 1225 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.24(3H), 8.90(d, $J=6.5$ cps), 8.88, 8.01(3H), 7.29(1-2H), 6.48(3H), 6.40(3H), 5.08(1H, broad), 4.87(1H).

The oily acetoxy diester 110b (50 mgs) was dissolved in 5 mls of anhydrous methanol containing 1.7 mmoles of sodium methoxide. After

standing for 12 hours at room temperature the solution was diluted with water and extracted three times with methylene chloride (total vol. = 75 mls). The combined methylene chloride extracts were washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. Several recrystallizations from Skellysolve provided the n.m.r. and infrared samples of 116, m.p. 98-103°C. Infrared spectrum: $\checkmark_{\max}$ 3610(sharp), 3510(broad), 1710(s), 1220 cm^{-1} (m). Nuclear magnetic resonance spectrum: γ 9.24(3H), 8.91(3H, $J=6.8$ cps), 8.84(3H), 8.28(1H), 7.68(1H, multiplet), 7.32(1H, $J=4$ cps), 7.03(1H), 6.41(3H), 6.34(3H), 5.90(1H, broad), 4.82(1H, d, $J=1.6$ cps).

Deuterium exchange removed the hydroxyl absorption in the n.m.r. (8.28 γ), and infrared spectra, being replaced in the latter case by bands at 2670 cm^{-1} (sharp) and 2600 cm^{-1} (broad). Further purification of 116 provided the mass spec. sample, m.p. 101-103°C. Molecular ion at $m/e = 418$; other peaks at 403(1.3%), 388(0.9%), 358(1.2%), 341(0.8%), 325(1%), 316(1.6%), 121(3.0%, base peak).

The major acetoxy dimethyl ester 109b was purified by two additional chromatographies of the benzene-Skellysolve B fractions of chromatography #2. The oily acetoxy diester, purified in this manner was homogenous to t.l.c. analysis. Infrared spectrum: $\checkmark_{\max}$ 1714-25(s), 1226 cm^{-1} (s). Nuclear magnetic resonance spectrum: γ 9.38(3H), 8.92($J=6.5$ cps), 8.89, 8.00(3H), 7.32(1-2H, broad), 6.45(3H), 6.40(3H), 5.55(1H, broad), 4.66(1H).

The infrared spectrum was identical with that of the acetoxy diester prepared from lactone II.

Zemplin methanolysis of 109b was carried out as described for 110b. The hydroxy dimethyl ester 112 crystallized immediately on seeding

with a sample prepared from lactone II, m.p. 135–136°C after several recrystallizations from benzene-Skellysolve and methanol-water. The infrared and n.m.r. spectra were identical with those obtained from lactone II. Mixture melting point was underpressed.

In another experiment the monoacid 41 (5.0 g., 112 mmoles) was decarboxylated as above, the oily product filtered through acid-washed alumina and converted with sodium methoxide in methanol to 1.28 g. (27% yield) of crystalline material, m.p. 110–118°C, after one recrystallization from Skellysolve. Several recrystallizations raised the melting point to a constant value of 119–120°C. The preparation was homogenous to t.l.c. analysis but from its n.m.r. spectrum was found to be a 2:1 mixture of 112 and 116. The infrared spectrum was identical with that of the mixture isolated during the chromatographic purification described in the main experiment.

e) Reactions of the hydroxy diester 112

i. Oxidation to the keto diester 113

Hydroxy dimethyl ester 112 (0.058 g., 0.14 mmoles) was dissolved in 5 mls of acetic acid, 0.12 mls of Kiliani reagent (0.09 mmoles) added and the solution stirred at room temperature for 70 minutes. Excess oxidant was then destroyed with methanol, the reaction mixture diluted with water and extracted several times with chloroform. The combined extracts (30 mls) were washed with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization from methanol and Skellysolve B provided the pure keto dimethyl ester 113, m.p. 160.6–161.5°C. Calc. for $C_{25}H_{36}O_5$: C, 72.07; H, 8.72; O, 19.21%. Found: C, 72.16; H, 8.46; O, 19.28%. Infrared spectrum: $\checkmark_{\text{max}}^{CHCl_3}$ 1722(sh),

1705(s), 1220-40 cm^{-1} (s). Nuclear magnetic resonance spectrum: γ 9.32 (3H), 8.95(6H, $J=7$ cps), 8.84(3H), 7.17(1H), 6.88(1H, broad), 6.38(3H), 6.34(3H), 4.29(1H). Ultraviolet spectrum: $\lambda_{\text{max}}^{\text{isooctane}}$ 282($\epsilon = 120$), 296($\epsilon = 139$), 305($\epsilon = 122$), 318($\epsilon = 61$). R.D. in isooctane ($c = 0.168$) negative Cotton effect curve $[\alpha]_{\text{D}}^{-120^\circ}$ $[\alpha]_{500}^{-191^\circ}$ $[\alpha]_{400}^{-595}$ $[\alpha]_{350}^{-1430}$ $[\alpha]_{317}^{-5620}$ (trough) $[\alpha]_{311}^{-4400}$ $[\alpha]_{307}^{-4800}$ $[\alpha]_{300}^{-1440}$ $[\alpha]_{295}^0$ $[\alpha]_{280}^{+5450}$.

The keto diester 113 could be conveniently prepared by oxidizing a mixture of the hydroxy diesters 112 and 116 according to the procedure described above. One recrystallization of the crude oxidation product from Skellysolve provided a 45% yield of the keto diester, m.p. 143-153°C. Further recrystallization from methanol and benzene-Skellysolve gave the purified sample identical with the keto ester prepared from 112 by infrared and mixture melting point determination.

- ii. Attempted conversion of the hydroxy dimethyl ester to the unsaturated ester.

Sodium metal (0.117 g., 5.1 moles) was dissolved in 6 mls. of anhydrous methanol. Hydroxy diester (0.008 g.) was added and the solution refluxed five hours, protected from atmospheric moisture with a CaSO_4 drying tube. Benzene was then added, the solution washed several times with water, dried over anhydrous magnesium sulfate, filtered and evaporated. One recrystallization from Skellysolve provided 2.4 mgs of starting material, m.p. 134-137°C.

- iii. Attempted saponification of the hydroxy diester 112 to the hydroxy acid 111.

The hydroxy diester 112 (0.132 g., 0.32 mmoles) was dissolved in

3.0 mls of dioxane, 2.0 mls of aq. sodium hydroxide (0.25 molar, 0.5 mmoles) added and the solution heated four hours at reflux. Dilute aq. HCl was then introduced and the organic precipitate taken up in methylene chloride, washed with distilled water, dried over anhydrous magnesium sulfate and evaporated. Two recrystallizations of the solid residue from Skellysolve gave needles, m.p. 132-136°C, shown to^{be} starting material by infrared and m.m.p. determination.

f) Oxidation of the rearranged alcohol 116 with Kiliani reagent.

The hydroxy diester 116 (0.013 g., 0.032 mmoles) was dissolved in 4 mls of acetic acid containing 0.05 mls of Kiliani reagent (0.035 g., 0.04 mmoles). The reaction mixture was stirred at room temperature for one hour, then diluted with water and extracted several times with methylene chloride. Evaporation of the methylene chloride extracts gave an oil which could not be crystallized either before or after chromatography on neutral alumina. The chromatographed material (2-3 components by t.l.c. analysis) possessed the following spectral characteristics. Infrared spectrum (semi-micro cell): $\nu_{\max}$ 1710 cm^{-1} (s). Ultraviolet spectrum: $\lambda_{\max}^{\text{isooctane}}$ 298($\epsilon = 141$), 308($\epsilon = 112$), 318($\epsilon = 73$), R.D. in isooctane ($c = 0.040$), positive Cotton effect curve: $[\alpha]_D +145$

$[\alpha]_{500}^{+235}$ $[\alpha]_{400}^{+515}$ $[\alpha]_{350}^{+1085}$ $[\alpha]_{319}^{+3290}$ $[\alpha]_{313}^{+2650}$
 $[\alpha]_{309}^{+2825}$ $[\alpha]_{300}^{+1680}$ $[\alpha]_{289}^0$ $[\alpha]_{280}^{-2240}$.

g) Conversion of the keto dimethyl ester 113 to the deoxy derivative 114

The keto diester 113 (0.400 g., 0.96 mmoles) was dissolved in 15 mls of ethanol-free chloroform. The solution was then saturated with

anhydrous HCl, 2.5 mls of ethanedithiol added, and allowed to stand four days at room temperature. At the end of this period the solution was diluted with benzene (150 mls), washed several times, first with dil. aq. K_2CO_3 , then with distilled water, and the benzene evaporated. The oily residue was dissolved in 50 mls of 95% ethanol and refluxed 10.5 hours with 4 g., of W-2 Raney nickel. The nickel was then filtered off, washed with ethanol, and the filtrate evaporated. The residue was taken up in methylene chloride, filtered free of an amorphous water-soluble solid and the filtrate evaporated. The colourless oil obtained (.330 g.) was chromatographed on 10 g. of neutral alumina. Elution with Skellysolve (200 mls) and benzen-Skellysolve (1:20, 100 mls; 1:10, 200 mls) provided traces of uncharacterized oils. Elution with benzene-Skellysolve (1:3, 250 mls; 1:1, 400 mls) and benzene (150 mls) yielded 0.110 g. (27% yield) of the crystalline deoxy diester 114. Continued elution with benzene and benzene-ether (3:1) yielded oils which were not examined further.

The diester 114, m.p. 69-69.5, was purified by recrystallization from methanol-water. It was found to be identical by melting point, mixture melting point, n.m.r. and infrared comparison, with the adduct derived from the Diels Alder reaction between methyl levopimarate and methyl acrylate. Calc. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52; O, 15.90%. Found: C, 74.74; H, 9.59; O, 16.01%. Infrared spectrum: $\nu_{\max}^{\text{nujol}}$ 3035(w), 1724(sh), 1718(s), 1250 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.38(3H), 8.94(6H, $J=7$ cps), 8.84(3H), 6.42(3H), 6.32(3H), 4.64(1H). Mass spectrum: molecular ion at $m/e = 402(1.4\%), 316(3.5\%), 146(4.9\%), 133(3.6\%), 121(4.5\% \text{ base peak}), 101(3.1\%)$.

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